DOES NOT CIRCULATE
UNIVERSITY OF MICHIGAN
MAY 19 1955
MEDICAL LIBRARY

The Journal of Obstetrics and Gynaecology of the British Empire

Issued under the Direction of the Royal College of Obstetricians and Gynaecologists

EDITOR
JAMES YOUNG

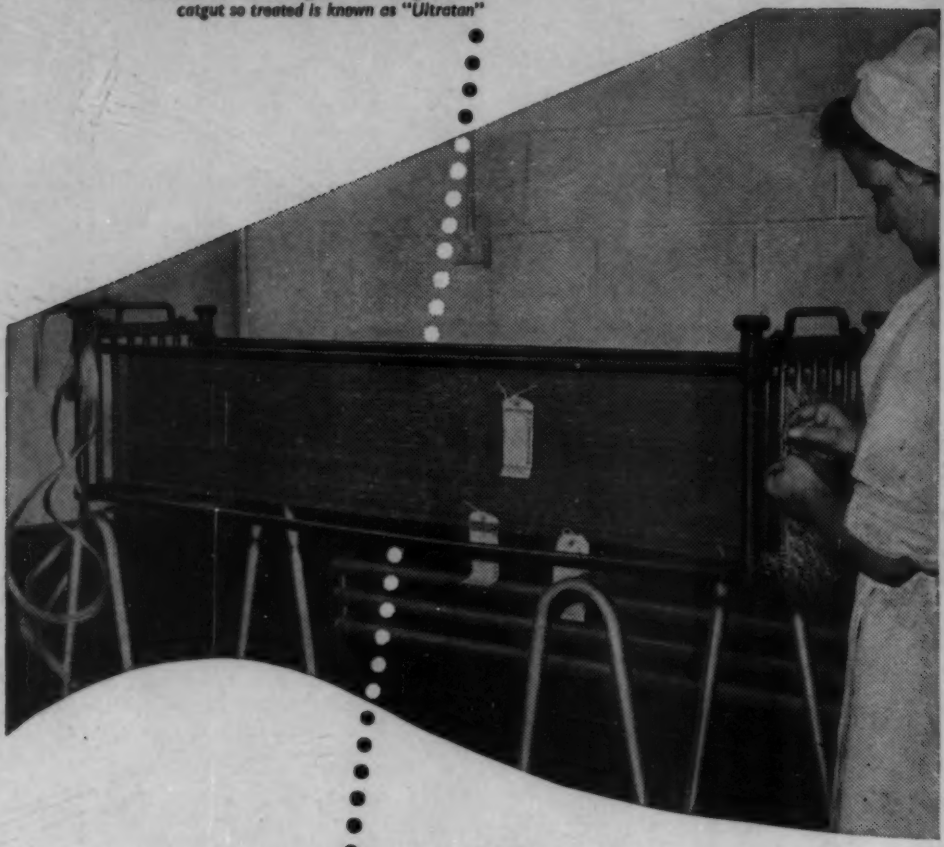
EDITORIAL REFERENCE COMMITTEE
DUGALD BAIRD J. C. McCLURE BROWNE
S. G. CLAYTON

All Business Correspondence to
The Journal of Obstetrics and Gynaecology
of the British Empire
58 Queen Anne Street, London, W.1

All Editorial Correspondence to
Prof. James Young
Ashfield, Balcombe Road,
Haywards Heath, Sussex

VOL. LXII, No. 2 APRIL 1955 PRICE 12*s.* 6*d.* NET

Manufacturing LHC. Stage 8. Each strand of catgut is independently strung on a special frame before immersion in the Hardening baths. This ensures even absorption. At the London Hospital two baths are used to effect Hardening, and the catgut so treated is known as "Ultratan"



London Hospital Catgut
is manufactured under unified control from intestine to sterile tube

Specify LHC OBTAINABLE FROM ALL LEADING SURGICAL EQUIPMENT HOUSES

WHG8

The Journal of
Obstetrics and Gynaecology of the British Empire

VOL. LXII, No. 2 NEW SERIES APRIL 1955

A STUDY OF THE EFFECTS OF DIHYDROERGOTAMINE ON THE INTACT HUMAN UTERUS

Part I—"Sympatholytic" Properties

BY

WILLIAM J. GARRETT, M.B., B.S.

Nuffield Department of Obstetrics and Gynaecology, University of Oxford

THE aetiology of incoordinate uterine action remains obscure. Excess endogenous adrenaline and over-action of the uterine sympathetic nerves may be contributing factors, so in recent years the use of an adrenaline blocking drug has been suggested as the logical therapeutic measure to be applied in such cases. With this theory in mind, dihydroergotamine has held favour with some workers as it is said to possess powerful adrenaline-blocking properties yet to be devoid of the oxytocic activity characteristic of the ergot series as a whole—an activity which is potentially dangerous in labour because of the unpredictable spasm which it may produce.

Crude ergot extracts were first shown to antagonize the effects of adrenaline by Dale in 1906. In cats, dogs and ferrets he showed that, after the administration of ergot, adrenaline failed to produce the customary rise in blood pressure, and in many instances caused an actual fall from the resting level. With the uterus of those species in which adrenaline normally produced stimulation (rabbit, monkey and pregnant cat), he found that adrenaline caused relaxation after the administration of ergot. In the non-pregnant cat, however, adrenaline caused relaxation of the uterus both before and after the administration of ergot.

In succeeding years the active alkaloids were isolated one by one from crude ergot. These were shown to possess in varying degrees both the oxytocic and adrenaline-blocking characteristics of the crude preparation; the latter property was strongest in the case of ergotoxine and ergotamine and weakest in the case of ergometrine.

After the semi-synthetic dihydroergotamine was elaborated by Stoll and Hoffman (1943) it also was found to have powerful adrenaline-blocking properties (Rothlin, 1947). At that time dihydroergotamine was supposed to lack the direct oxytocic properties of the other ergot alkaloids, and so was used by Sauter (1948) in incoordinate human labour for its adrenaline-blocking properties, to counter the alleged over-action of the sympathetic nervous system. Reist (1949) and Gill and Farrer (1951) reported favourably on further cases. In each of these series the clinical response observed was attributed to the "sympatholytic" properties of the drug—an assumption based on animal experiment alone.

Recently, Garrett (1955) showed *in vitro* that both adrenaline and noradrenaline stimulated excised human myometrium to contract, and that this stimulation could be blocked by dihydroergotamine—an observation in keeping with previous experimental work in other excised mammalian uteri. Despite this evidence with excised human tissue, it does not follow that dihydroergotamine will exert similar adrenaline-blocking and noradrenaline-blocking properties in the parturient patient, because

these latter two hormones have opposite actions *in vivo*. Noradrenaline has been shown by Kaiser (1951) and Garrett (1954) to stimulate uterine contractions in labour, while adrenaline has been demonstrated to inhibit them.

Gaddum (1950) has pointed out that, as a general rule, the ergot alkaloids block the motor or α effects of adrenaline more readily than they do the inhibitor or β effects. Therefore, from the evidence that dihydroergotamine easily blocks the adrenaline-*stimulation* of excised strips of myometrium, it may not follow that it will similarly block the adrenaline-*inhibition* seen in the intact labouring uterus.

To clarify this point as to the mode of action of dihydroergotamine *in vivo* it was proposed to examine the effects of adrenaline and noradrenaline on the intact human uterus before and after the administration of a "sympatholytic" dose of dihydroergotamine.

I. Late Pregnancy and Labour

Method

Following the method previously described (Garrett, 1954), *l*-adrenaline (as the hydrochloride) or *l*-noradrenaline (as the bitartrate) was given to 9 healthy patients in late pregnancy or labour by very slow intravenous infusion. The effect of the drug on the spontaneous uterine contractions was recorded by inserting a small hydrostatic bag into the uterus, to lie outside the membranes and above the foetal head. This was connected to a mercury manometer recording on a kymograph.

After the characteristic response to a test-dose of adrenaline or noradrenaline had been noted, and the uterine activity had returned to normal, an injection of dihydroergotamine methanesulphonate was given. The doses employed were those recommended by Gill (1953) and Bruns, Snow and Drose (1953) as being adequate to produce the required effect, and also the maximum that can be given with safety, viz., 0·25 mg. by intramuscular injection, and 0·1 mg. per ½-hour by slow intravenous infusion, respectively.

At a suitable time later, the intravenous infusion of adrenaline or noradrenaline was repeated and its effects were once again noted.

Results

(i) *D.H.E. by intramuscular injection:* After a test-dose of adrenaline, 3 patients were given 0·25 mg. dihydroergotamine methanesulphonate by intramuscular injection. The intravenous infusion of adrenaline, when repeated 30–60 minutes later, produced the characteristic effect of adrenaline unaffected by the previous administration of dihydroergotamine (Fig. 1).

Similarly, 3 patients were given noradrenaline by very slow intravenous drip infusion before and after the intramuscular injection of 0·25 mg. dihydroergotamine methanesulphonate. In these patients, too, no difference was noted in the uterine response to noradrenaline before and after the injection of dihydroergotamine (Fig. 2).

(ii) *D.H.E. by intravenous injection:* Three patients were given dihydroergotamine by this method. When, after a test-dose of adrenaline, the uterine activity had returned to normal, an intravenous drip apparatus was set up to deliver dihydroergotamine methanesulphonate at the rate of 0·1 mg. per ½-hour. After this latter drip infusion had been running for 20–30 minutes, the test-dose of adrenaline was repeated by connecting the two sets of drip apparatus to the one needle so as to give both adrenaline and dihydroergotamine concurrently.

In each case, as soon as the adrenaline infusion was recommenced the spontaneous uterine contractions were again inhibited (Fig. 3). In one case only, the second response to adrenaline, while present, was not as great as the control test-dose.

None of these 9 patients complained of symptoms during the administration of the drugs. However, with both adrenaline and noradrenaline the customary physical signs (raised blood pressure, altered heart rate, hyperpnoea, etc.), were noted.

II. Puerperium

One patient was examined in the puerperium. Following the method first described by Moir (1932), the small balloon used in earlier experiments in this paper was inserted into the uterine cavity on the sixth puerperal day.

In the control period the uterus was virtually

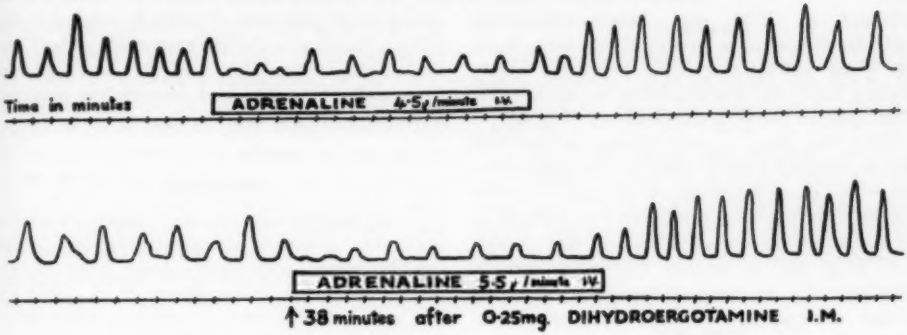


FIG. 1

The uterine response to slow intravenous infusion of Adrenaline is unaffected by intramuscular injection of 0·25 mg. Dihydroergotamine methanesulphonate.

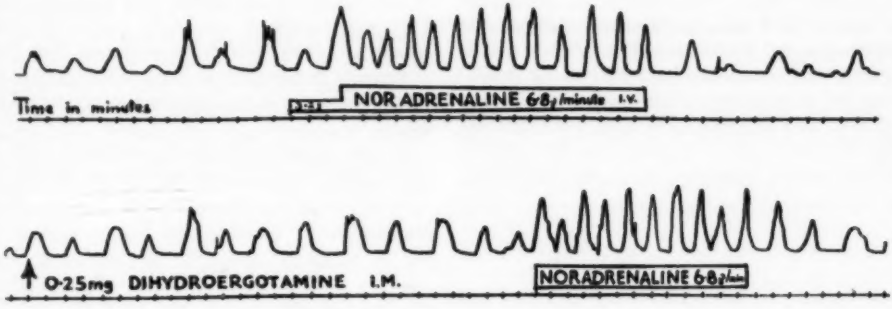


FIG. 2

The uterine response to slow intravenous infusion of Noradrenaline is unaffected by intramuscular injection of 0·25 mg. Dihydroergotamine methanesulphonate.

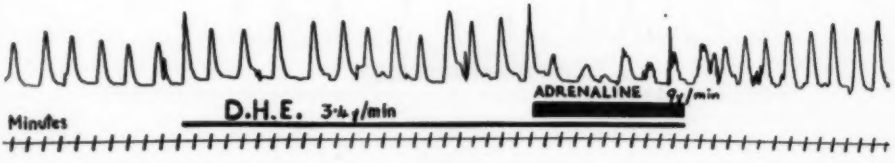


FIG. 3

Inhibition of uterine contractions by Adrenaline is seen during the slow intravenous infusion of Dihydroergotamine methanesulphonate at the rate of 0·1 mg. per half hour.

quiescent so 0·75 mg. dihydroergotamine methanesulphonate, a comparatively large dose, was given by intramuscular injection. Thirty minutes later the characteristic oxytocic effect of this dose of the drug was observed (Fig. 4a).

When this drug-induced uterine activity was well established a small dose of adrenaline was given by slow intravenous infusion for 19 minutes. During this period the amplitude of the observed uterine contractions was diminished (Fig. 4b) in exactly the same way as adrenaline acts on the spontaneously occurring uterine contractions of late pregnancy and labour (Garrett, 1954).

In view of the animal experiment with dihydroergotamine by Orth and Ritchie (1947) and White, Noltensmeyer and Morris (1951), who showed that the drug could protect against adrenaline-induced cardiac arrythmias, the general symptoms produced in this patient were of interest. With 4 micrograms of adrenaline per minute for 2 minutes there was symptomless tachycardia and hyperpnoea but as soon as the infusion was cautiously increased to 12 micrograms per minute the patient became pale, began to shiver, and said she felt scared. On examination, the pulse rate was below 60 per minute and was grossly irregular in time and amplitude owing to the presence of multiple extra-systoles. After about 2 minutes the symptoms of fear and cold abated somewhat and the extra-systoles became less frequent, but nevertheless persisted until the infusion was withdrawn.

Discussion

From clinical experience of many cases the maximum doses of dihydroergotamine which can be given with safety have been clearly formulated (Gill, 1953; Bruns *et al.*, 1953). It has been assumed that the response observed to these doses of dihydroergotamine in labour is due to the capacity of that drug to block sympathetic nervous influences. The word "sympatholytic", a poorly contrived term, has been commonly used to describe both the blocking of impulses at the sympathetic nerve endings, and also the pharmacological blocking of the action of adrenaline and noradrenaline. This assumption is probably justifiable since Mann and West (1951) have shown that both adrenaline and noradrenaline are liberated at the sympathetic nerve endings in the uterus of the cat.

In this paper evidence is produced that, in the maximum dosage permissible in the human

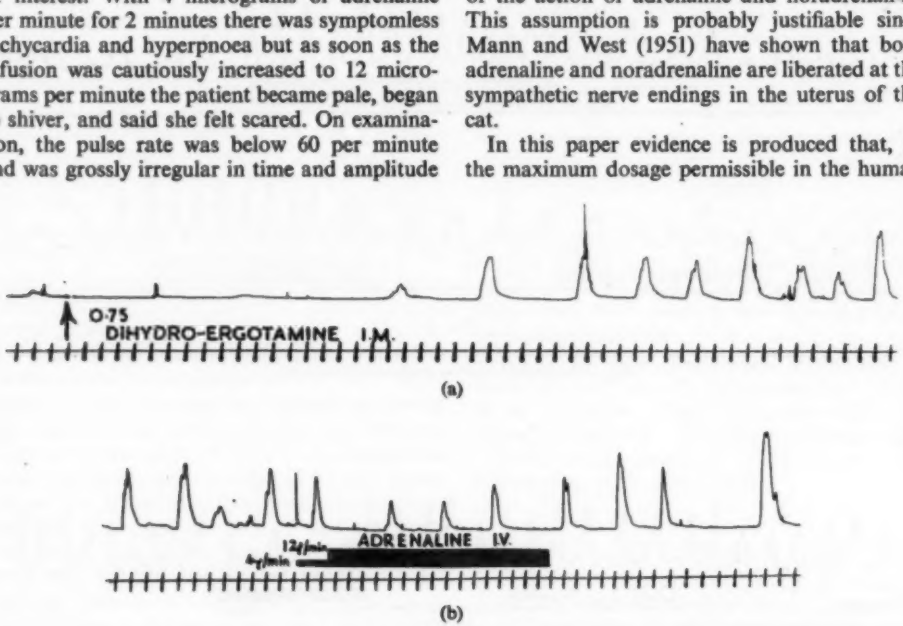


Fig. 4

(a) Intramuscular injection of 0·75 mg. Dihydroergotamine methanesulphonate induces uterine activity on the 6th day of puerperium.

(b) This drug-induced activity is inhibited during a slow intravenous infusion of Adrenaline.

subject, dihydroergotamine fails to impede the normal response of the body of the uterus to the adrenal medullary hormones. After intramuscular injection of 0·25 mg. dihydroergotamine both adrenaline and noradrenaline still have their characteristic effects on the uterus in late pregnancy and labour; in the presence of 0·1 mg. dihydroergotamine per ½-hour by slow intravenous infusion uterine contractions are still inhibited by adrenaline.

In these experiments the doses of adrenaline and noradrenaline were within physiological limits as no subjective symptoms were produced. It is difficult, therefore, to reconcile any effect that dihydroergotamine may have on the uterus as being by virtue of a specific sympathetic-blocking mechanism. Perhaps larger doses of dihydroergotamine would have this action, but these will be shown in a separate communication to be dangerously oxytocic (Embrey and Garrett, 1955).

Finally, to press this matter to a conclusion, three times the dose of dihydroergotamine regarded as a "safe intramuscular dose" for a woman in labour, was given to a patient in the puerperium. When this had induced uterine contractions in a previously quiescent uterus, it was found that these contractions (actually produced as a "toxic" manifestation of dihydroergotamine) could be inhibited by adrenaline. How then can we consider the drug to be "sympatholytic"?

These findings are further backed by the appearance in this latter patient of extrasystoles and other toxic signs with a small dose of adrenaline despite the previous injection of dihydroergotamine.

Summary

(1) Statements have been made in clinical publications that dihydroergotamine acts in the intact human uterus as a sympathetic-blocking agent.

(2) From the human subject in late pregnancy and labour, direct tocographic evidence has been produced showing that dihydroergotamine fails to block the actions both of adrenaline and of noradrenaline in the doses recommended by its advocates.

References

Bruns, P. D., Snow, E. H., and Drose, V. E. (1953): *Obstet. Gynec.*, **1**, 188.

Dale, H. H. (1906): *J. Physiol.*, **34**, 163.

Embrey, M. P., and Garrett, W. J. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 150.

Gaddum, J. H. (1950): *Proc. roy. Soc. B.*, **137**, 292.

Garrett, W. J. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 586.

Garrett, W. J. (1955): *Brit. J. Pharmacol.*, **10**, 222.

Gill, R. C. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 103.

Gill, R. C., and Farrer, J. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 79.

Kaiser, I. H. (1951): *Surg. Gynec. Obstet.*, **90**, 649.

Mann, M., and West, G. B. (1951): *Brit. J. Pharmacol.*, **6**, 79.

Moir, C. (1932): *Brit. med. J.*, **1**, 1022.

Orth, O. S., and Ritchie, G. (1947): *J. Pharmacol.*, **90**, 166.

Reist, A. (1949): *Schweiz. med. Jahrb.* Schwabe, Basle. p. 41.

Rothlin, E. (1947): *Bull. Acad. suisse Sci. méd.*, **2**, 249.

Sauter, H. (1948): *Schweiz. med. Wschr.*, **78**, 475.

Stoll, A., and Hoffman, A. (1943): *Helv. chim. Acta*, **26**, 2070.

White, S. M., Noltensmeyer, M. H., and Morris, W. E. (1951): *Arch. int. Pharmacodyn.*, **88**, 361.

A STUDY OF THE EFFECTS OF DIHYDROERGOTAMINE ON THE INTACT HUMAN UTERUS

Part II—"Oxytocic" Properties

BY

MOSTYN P. EMBREY, M.D., B.Sc., F.R.C.S.E., M.R.C.O.G.

AND

WILLIAM J. GARRETT, M.B., B.S.

Nuffield Department of Obstetrics and Gynaecology, University of Oxford

THE identification and isolation of the alkaloids of ergot and their mode of action have been matters of great interest to pharmacologists and clinicians alike since the turn of the century. Beginning with the discovery of ergotoxine in 1906, followed by ergotamine in 1918, and with the notable landmark for clinicians of the identification of ergometrine by Dudley and Moir in 1935, the story has recently continued with the elaboration of the semi-synthetic alkaloid dihydroergotamine by Stoll and Hoffman in 1943.

This new drug was claimed to possess powerful sympatholytic properties; yet, despite its family relationship to the other ergot alkaloids, was alleged to have no direct oxytocic effect on the uterus.

The first report of its use in clinical obstetrics was from Sauter (1948) who commented favourably on its use in 43 cases of uterine inertia.

In 1951 Gill and Farrar further studied the new alkaloid. They compared its properties with those of ergotamine and ergometrine, and, in the belief that it was a sympatholytic drug devoid of oxytocic properties, used dihydroergotamine in 43 cases with uterine inertia. They reported favourably on its action and recommended its use particularly in cases of "hypertonic inertia" but advised that the dose should not exceed 0·25 mg. intramuscularly.

Reviewing the literature these authors quoted Orth and Ritchie's observation (1947) that dihydroergotamine had no oxytocic action in animal experiments. In rats, it was found that daily injection of dihydroergotamine throughout pregnancy was without effect on the gestation, labour or lactation—but in fairness it might have been added that Orth and Ritchie obtained exactly similar results with ergotamine, the oxytocic properties of which are not doubted.

Not all opinions expressed on the value of dihydroergotamine as an anti-spasmodic in incoordinate uterine action have been enthusiastic; and some workers have suggested that on occasion the drug may be oxytocic. In one case in this department the injection of 0·25 mg. of dihydroergotamine intravenously during labour was followed by violent uterine contractions, threatened tonic contraction and foetal distress; in another case 1 mg. by intramuscular injection produced like effects.

Other evidence that dihydroergotamine has undesirable effects has been produced by Altman, Waltman, Lubin and Reynolds (1952) who gave the drug by slow intravenous infusion to 20 patients in labour, and by external tocography demonstrated oxytocic activity. Almost certainly the dose used (1 mg. in 2–4 hours) was excessive, and it is significant that in the 20 deliveries there were 11 cases of foetal distress, 5 foetal deaths and 1 additional sub-dural haematoma, besides 3 cases of maternal haematuria.

More recently Bruns, Snow and Drose (1953) have also shown that dihydroergotamine by slow intravenous infusion has a motor effect on the parturient uterus. As a result of their experience, they recommended that the dose by this method should not exceed 0·1 mg. per ½-hour, lest untoward effects ensue.

Present Investigation

This study was undertaken to confirm or dispose of the clinical suspicion that dihydroergotamine may be directly oxytocic in action.

In his classical researches on the ergot alkaloids Moir (1932a, b) made use of two methods of recording the contractions of the puerperal uterus. His first method employing an intra-uterine balloon was an adaptation of that used by Bourne and Burn (1927) in labour, and was used to examine the actions of ergotoxine, ergotamine and other ergot preparations. Later it was employed in experiments which led to the identification of ergometrine.

The second was a method of external tocography using a modification of Dodek's apparatus (1932). Besides having the advantage of simplicity this apparatus could be used early in the puerperium without risk of sepsis, and so was employed when an exact record of intra-uterine tension was not necessary.

In the experiments to be described both methods of recording uterine activity have been employed. An internal method similar to that of Moir (1932a) has been used in the late lying-in period, while other records have been obtained using the external tocograph previously described by one of us (Embrey, 1955). This communication deals only with the effect of dihydroergotamine on the puerperal organ, the suitability of which as a test object for the study of oxytocic drugs was emphasized by Moir (1932a, b).

Results

Dihydroergotamine methanesulphonate was given to 26 healthy puerperal patients in varying amounts up to 1 mg. by both intravenous and

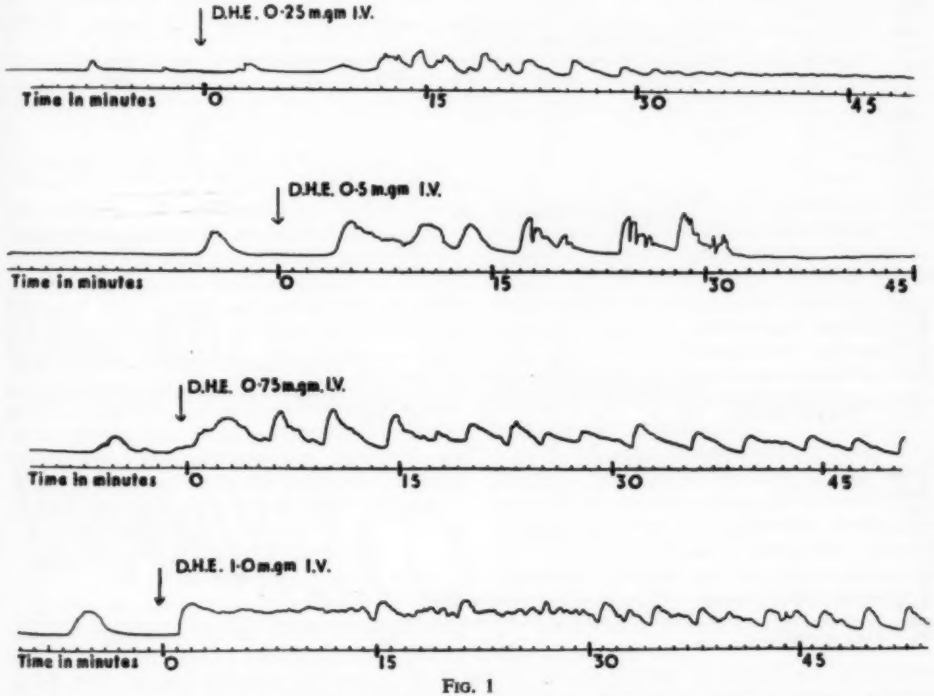


Fig. 1

The effect of varying doses of Dihydroergotamine by intravenous injection on the human puerperal uterus. (External recording.)

intramuscular routes. It can be said at once that the alkaloid was found to be very active in stimulating the uterine contractions, and there can be no doubt of its oxytocic properties. Typical responses are shown in Figs. 1 and 2.

Details and results of individual experiments are summarized in Table I.

In a dose of 0·1 mg. intravenously no definite effect was demonstrated, but 0·25 mg. and all larger amounts, whether by intravenous or intramuscular injection, produced an undoubted increase in uterine activity, almost without exception.

With the smaller doses (0·25 mg.) some variation in the character of the response was noted, but always the contractions were augmented in frequency and amplitude. The larger doses showed a more definite contraction pattern. The contractions were markedly increased in frequency and amplitude; with few exceptions there was with the larger doses an increase in uterine tone, as indicated by a rise in the base-line.

This uterine spasm was the result of a merging of rapid uterine contractions and was followed by a gradual return of the intra-uterine tension to normal—strong, regular but slower, isolated contractions taking the place of the spasm.

The time of onset and the duration of the effect of the drug naturally varied with the dose

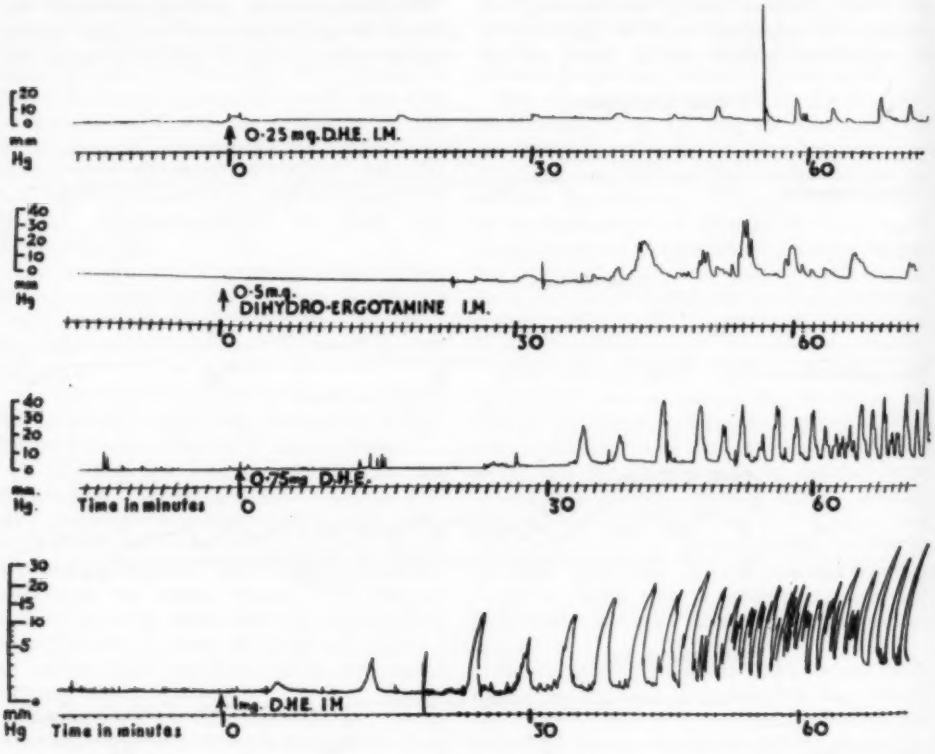


FIG. 2

The effect of varying doses of Dihydroergotamine by intramuscular injection on the human puerperal uterus. (Internal recording.)

TABLE I

Action of Dihydroergotamine methanesulphonate on the Puerperal Uterus

Dose	Intravenous Injection					Intramuscular Injection				
	Case No.	Oxytocic Response				Case No.	Oxytocic Response			
		Activity induced	Base-line raised	Time of onset (minutes)	Duration of activity (minutes)		Activity induced	Base-line raised	Time of onset (minutes)	Duration of activity (minutes)
0·1 mg.	1	0	0	Nil	Nil					
	2	0	0	Nil	Nil					
	3	0	0	Nil	Nil					
0·25 mg.	4	+	+	2	40	1	+	0	16	65+
	5	+	+	10	?	2	+	slightly	24	65+
	6	+	+	6	?					
0·5 mg.	7	+	+	2	?	3	+	0	31	30
	8	+	+	2	45+	4	0	0	Nil	Nil
	9	+	+	4	25					
	10	+	0	10	?					
	11	+	+	10	25					
0·75 mg.	12	+	+	2	40+	5	+	0	20	88+
	13	+	+	2	60	6	+	?	23	40+
	14	+	0	3	40+	7	+	+	33	50+
1·0 mg.	15	+	+	2	55	8	+	slightly	5	75+
	16	+	+	2	60	9	+	0	13	24
						10	+	slightly	16	75+

and method of administration. After intravenous injection 2–10 minutes elapsed before the effect of the drug was seen. By intramuscular injection an effect was produced in 15–40 minutes. The period of uterine spasm after intravenous injection usually lasted 15–30 minutes; this effect was less obvious after intramuscular injection. The total duration of action could not always be determined because of the limitations of time imposed on clinical experiment: after intravenous injection the effect mostly lasted 45–60 minutes, but after intramuscular injection it was usually longer.

COMMENTS

It will be noted that in its oxytocic effect dihydroergotamine closely resembles ergotamine and ergotoxine, having a comparable speed of onset but shorter duration of action. It is, howeves, noticeably slower to take effect and less powerful than ergometrine, and seems to be less uniformly reliable and consistent in its action. From these experiments the optimum dosage of dihydroergotamine for clinical use *as an oxytocic* in the third stage of labour, should that be desired, would be of the order of 0·75 to 1 mg. by intravenous injection, and twice this dose by intramuscular injection; but like ergotamine it is too slow in action to be suitable for clinical use, and in practice is not to be preferred to ergometrine.

In a separate communication, one of us (Garrett, 1955) described tocographic experiments in the human subject which showed that dihydroergotamine in permissible dosage does not have the specific adrenaline blocking properties generally ascribed to it. The results of the investigation now recorded demonstrate that the alkaloid is in fact a powerful, if somewhat erratic oxytocic.

It is impossible to avoid the conclusion, therefore, that any beneficial clinical response in hastening the course of protracted labour is

not a "sympatholytic" effect but is solely a direct oxytocic action of the drug.

Conclusion

Reviewing the history of dihydroergotamine one sees that its introduction to clinical practice was hailed as a boon in the treatment of uterine inertia (Sauter, 1948; Reist, 1949; Gill and Farrer, 1951). Later, with further experience, a note of caution was sounded (Altman *et al.*, 1952), and the dose to be used with safety was more clearly defined (Bruns *et al.*, 1953; Gill, 1953). In a recent investigation in the human subject the drug has failed to show an adrenaline-blocking effect (Garrett, 1955); and with the evidence presented in this paper, dihydroergotamine is demonstrated to possess, in common with many other ergot alkaloids, a direct oxytocic action.

Thus in one decade this new alkaloid has recapitulated in miniature the history of the crude ergot preparation which Stearns first introduced to clinical obstetrics in 1808. As the *pulvis parturiens*, the drug was at once proclaimed an infallible remedy for "lingering labour", but soon doubts were entertained regarding its safety, and by 1822 its evil reputation was such that Hosack, with gentle irony, proposed that the *pulvis ad partum* should be renamed the *pulvis ad mortem*.

So too with dihydroergotamine, if its action is solely that of a direct oxytocic, then from past experience it is to be eschewed as an adjuvant to labour, lest the unhappy history be repeated.

Summary

(1) The history of dihydroergotamine is reviewed. Hitherto it has been regarded as an adrenaline-blocking agent rather than a direct oxytocic drug.

(2) Tocographic evidence is produced from 26 healthy puerperal patients that dihydroergotamine is a powerful, though somewhat unreliable oxytocic agent.

(3) The dose of dihydroergotamine if used *as an oxytocic* in the third stage of labour, would be 0·75 to 1 mg. by intravenous injection, and at least twice as much by intramuscular injection; but for this use it does not appear to have any advantage over the better established alkaloids.

(4) The strong oxytocic properties of dihydroergotamine make it a potentially dangerous drug for the treatment of incoordinate uterine action in labour.

References

Altman, S. G., Waltman, R., Lubin, S., and Reynolds, S. R. M. (1952): *Amer. J. Obstet. Gynec.*, **64**, 101.

Bourne, A. W., and Burn, J. H. (1927): *J. Obstet. Gynaec. Brit. Emp.*, **34**, 249.

Bruns, P. D., Snow, R. H., and Drose, V. E. (1953): *Obstet. Gynec.*, **1**, 188.

Dodek, S. M. (1932): *Surg. Gynec. Obst.*, **55**, 45.

Dudley, H. W., and Moir, C. (1935): *Brit. med. J.*, **1**, 520.

Embrey, M. P. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 1.

Garrett, W. J. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 145.

Gill, R. C. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 103.

Gill, R. C., and Farrar, J. M. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 79.

Hosack (1822): Quoted by Barger, G. (1931): *Ergot and Ergotism*. Gurney and Jackson, London. p. 18.

Moir, C. (1932a): *Brit. med. J.*, **1**, 1022.

Moir, C. (1932b): *Brit. med. J.*, **1**, 1119.

Orth, O. S., and Ritchie, G. (1947): *J. Pharmacol.*, **90**, 166.

Reist, A. (1949): *Scheiz. med. Jahrb.* Schwabe, Basle. p. 41.

Sauter, H. (1948): *Schweiz. med. Wschr.*, **78**, 475.

Stearns, J. (1808): *Medical Repository of New York* (quoted by Barger, G. (1931): *Ergot and Ergotism*. Gurney and Jackson, London. p. 13).

Stoll, A., and Hoffman, A. (1943): *Helv. chim. Acta*, **26**, 2070.

UTERINE ACTIVITY AND ELECTRICAL RESPONSE

BY

E. C. HALLIDAY

National Physical Laboratory, Pretoria

AND

O. S. HEYNS

University of the Witwatersrand

INTRODUCTION

THE purpose of this paper is to examine statistically over 500 records of the electrical potentials observable when electrodes are applied to the abdominal skin of women during parturition. The study indicates that the potentials are a direct result of the activity of the uterus, and that the amplitude of the potentials has a close relation to the rate at which biological energy is being used during the contractions of labour. This finding is used to give direction to some clinical thoughts upon the phenomena of parturition.

HISTORICAL

In the past six years experiments have been reported by several research groups, in which electrical potential recordings have been obtained from electrodes placed upon the bodies of women in various stages of labour. Dill and Maiden (1946, 1948) made three-channel recordings from three electrodes placed respectively over the fundal, mid and lower segments of the uterus, with a common electrode placed on the thigh. Steer and Hertsch (1950) used a seven-channel recorder, so that not only could potentials be recorded from electrodes placed at three different places upon the abdomen of the patient, but in addition recordings of the change of contour during a uterine contraction could be obtained at three different points and coded observations of the experimenter could be added by means of the seventh channel.

Lévy-Solal, Morin and Zacouto (1952) observed potentials from a pair of electrodes, one on either side of the abdomen, described a potential pattern associated with uterine contraction and stated that the nature of the pattern varied with the type of labour, suggesting a mechanism whereby the different types of pattern were produced. In 1952 the present authors described similar experiments with electrical recordings and stated tentatively that there was evidence to support the view that the most usual mode of contraction of the uterus was an all-over equal contraction of muscle producing a hydrostatic pressure within the amniotic sac. Steer has produced a further paper (1954) in which the occurrence of potential "waves" with a frequency of about one a second and an amplitude of 0·25 millivolt during the period of a uterine contraction are described, the variations of this pattern being related to different clinical conditions during labour.

Since 1952 the present authors have made regular potential measurements in the labour ward of the Queen Victoria Hospital, and over 700 recordings have been secured. Of these, some have been made in the antenatal period and others during the third stage of labour, but approximately 500 records have been made upon women in the first and second stages of labour. The patients were not specially selected but observed as opportunity offered during the normal working of the hospital, and thus are probably a fair cross-section of the patients who are treated at the hospital. With 500 records to work upon it becomes possible to use the statistical method, in order to study the relationship of the observed potentials to the clinical picture of the type of uterine action. The following lines of study have been followed:

(i) It was suggested in the 1952 paper that the potential was in some way a measure of the rate at which chemical energy was being expended. Thus it might be expected that if a labour was hard, in the sense that very energetic muscle contractions were necessary, then the potentials produced during each uterine contraction should be larger than in the usual run of cases. On the other hand, in a multipara with a record of short and easy deliveries the potentials might be expected to be smaller than in the usual run of cases.

(ii) The condition known as inertia, in which dilatation of the os is very slow, is sometimes considered to be due to inactivity of the uterus. This postulated inactivity might be reflected in the potential records from such cases.

(iii) The three trace recordings from the fundus, the mid segment and the lower segment made it possible to see if there was any indication of polarity in the uterine action, or of a gradient of activity such as is described by Reynolds (1949).

Statistical Study

Because of the considerable variation in average amplitude of the different records and their change in amplitude during the half to one hour of the recordings, it was decided, for this study, not to attempt a numerical assessment of potential amplitude and a study of these figures by statistical means, but to use the method of dividing the records into three general classes in which the amplitude of the potential peaks was large (over 6 mv.), small (under 3 mv.), and medium (between 6 and 3 mv.).

The first test was based upon the general observation that primigravidae on the average have a longer labour, and many think a harder labour than multiparae: the three groups were each divided into those who were primigravidae and those who were not. Table I gives the results of this division. The three large headings give the groupings according to amplitude of potential recorded, and under each of these headings there are three columns. In the first column is the number of cases observed, the first number giving the primigravidae and the second number the multiparae. In the second column under each large heading is given the number of cases which would be expected in that category, on the assumption that the amplitude of the potential observed had no causal connexion with the parity of the patient. This "expected cases" figure can be obtained by simple proportion. From the last isolated column of totals it will be seen that there were 282 primigravidae and 185 multiparae. If there is no relationship between parity and amplitude, then the cases in the three groupings should be divided into multiparae and primigravidae in the proportion of 185 to 282. This was done to the nearest whole number and the figures in the "expected cases" columns were obtained. When the table is observed, it is seen that for the medium and small potentials the actual numbers of cases observed are fairly close to the expected numbers. Under the heading of "large potentials", however, there are more primigravidae than expected and fewer multiparae than expected, indicating that primiparae tend to have higher potentials than do multiparae. In order to test the reliability of this deduction we make use of the χ^2 test, in which the difference between the observed and expected number of cases is squared and then divided by the expected

Table I

Effect of Parity on Potential Amplitude

Class	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
Primigravidae	71	59	3·4	94	97	0·1	117	124	0·3	282
Multiparae ..	27	39	3·7	68	65	0·1	90	83	0·8	185

number of cases. If this derived number is greater than a value which, for the type of table here constructed, is 6, there is a 95 per cent chance that the figures show a real dependence of potential on parity. The deduction from the table is that multiparae tend to have lower potentials than do primigravidae.

It was suggested previously (Halliday and Heyns, 1952) that the potentials which are being registered are in some way related to the magnitude of the chemical changes associated with uterine contractions, and, if it is true that the primigravida does more work in labour than the multipara, then the explanation of the high potentials associated with the primigravida may lie in this direction.

A second examination of the records was made by dividing them into those cases which took over 24 hours to deliver, those which took between 24 and 8 hours, and those which took less than 8 hours. The evidence is shown in Table II, and here the set out is almost the same as in Table I, except that, as there are now three rows as well as three headings, the value of χ^2 must be 9 before there can be a 95 per cent chance that the differences between actual and expected cases are statistically significant.

It will be seen from the table that patients taking more than 24 hours to deliver show large potentials more frequently than is to be expected, but that patients taking less than 8 hours also show large potentials more frequently than is to be expected, while the general run of patients show high potentials rather less frequently. The total value of χ^2 for the table is 14, indicating that there is a considerable degree of significance in these deviations, but as the large potentials appear more frequently with both the unusually long and the unusually short labours it would appear that there are two processes operating which have not been separated. If it is true that a large potential implies a greater expenditure of biological energy, then it is not always true that a great expenditure of biological energy will lead to a short labour: it may actually imply a long labour.

A type of case in which it might definitely be expected that very little energy is being expended is the person suffering from inertia, where there is a very slow dilatation of the cervix accompanied by either lack of tone or else by continuous high tone in the uterus. Table III shows an analysis of the cases which were considered by the doctor in charge to be true inertias. From this

TABLE II

Effect of Duration of Labour on Potential Amplitude

Class	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
>24H ..	26	18	3·5	32	32	0	30	39	2·0	88
24–8H ..	55	68	2·5	110	112	0	159	144	1·6	324
<8H	17	12	2·1	20	18	0·2	18	24	1·5	55

TABLE III

Effect of Inertia on Potential Amplitudes

Class	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
Inertia ..	15	11	1·4	24	21	0·4	18	24	1·5	57
Normal labour	81	85	0·2	159	162	0·0	190	184	0·2	430

table it is clear that inertia as a clinical feature does not affect the magnitude of the potentials observed.

Another way in which the relation between uterine work and potential output may be studied is by considering the development of the uterine action as the labour progresses. Table IV has been constructed by collecting into four categories: (*a*) those cases where the clinical opinion was that the patient was in false labour and this was confirmed by the patient being sent home or else having a recession of labour and delivering a day or two later; (*b*) those cases in which the recording was made while the patient was in the first third of the first stage; (*c*) those cases where the patient was in the second third of the first stage; and (*d*) cases recorded during the last third of the first stage. A study of the table shows that for those patients in false labour there was an excess of cases showing small potentials and a deficit of cases showing high potentials. During the first third of the first stage there is still an excess of cases showing small potentials and a deficit of cases showing large potentials but by the second third of the first stage this position has been reversed and the trend continues into the last third of the stage. The total value of χ^2 for the table is 20 indicating a very high significance for these changes. It thus appears, that if the clinical impression is correct that labour pains steadily strengthen during the course of labour, this increase in muscular activity is accompanied by an increase in the recorded potential waves.

A further line of study is presented by the log kept by the assistant who made the recordings in the labour ward. This assistant stayed with the patient throughout the recording, noting everything which happened in the ward and sometimes making a note when it appeared that the patient was suffering considerably more than most other patients. This log was used to divide the cases into (*a*) those who were having an average sort of labour, and (*b*) those who, by their demeanour, were having a hard labour. As might be expected, not many of the 500 women qualified for the observation that they were having an unreasonably hard labour during the first stage. Table V, however, shows that these cases do show a considerable agreement with

TABLE IV

Effect of Progress of Labour upon Potential Amplitude

Stage	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
False labour ..	13	24	5·0	50	47	0·2	61	53	1·2	124
1st third ..	7	10	0·9	15	20	1·2	30	22	2·9	52
2nd third ..	25	21	0·8	33	40	1·2	48	45	0·2	106
Last third ..	51	41	2·4	85	78	0·6	69	88	4·1	205

TABLE V

Hard Labour and Potential Amplitude

Class	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
Normal labour	78	85	0·6	164	162	0·1	189	184	0·1	431
Hard labour ..	18	11	4·5	19	21	0·2	19	24	1·0	56

the evidence produced by the potential patterns.

It will be noticed that in the case of the hard labours, 11 were expected to show large potentials, whereas actually 18 did so—an 80 per cent increase—while for the small potentials there is a deficit of 5 cases or 20 per cent. The table, when assessed by the χ^2 test, gives a figure of 6·4 indicating a 95 per cent chance that the increase in electrical potential is actually related to the severity of the labour.

When tables were drawn up to study the evidence of the records for a gradient of activity along the uterus, or for a dominance of fundal activity over cervical or lower segment activity, no such evidence could be found. A large number of tables was constructed, to relate such cases of dominance as were found to a large number of clinical factors in labour, but in no study could any relationship be found. It was then decided to leave the matter for some further investigation and to report upon this somewhat complex situation at a later time. We report at the present moment only the fact that records were obtained where the fundal potentials were higher than the lower segment potentials, but we also obtained records in which the opposite condition prevailed. By far the larger number of records, however, showed the potentials from all three regions of the uterus to be practically of equal amplitude, so that the evidence, while somewhat confused, is against any idea of fundal dominance in uterine activity.

Discussion of Results

On the basis of the analysis in Tables I, IV and V it may be said that there is some support for the theory that the potentials being observed are an indication (even if indirect) of the expenditure of biological energy in the process of labour. Therefore, it is possible to suggest that when no potentials are observed the patient is not in true labour and that the contractions will not produce dilatation of the cervix, even though the abdomen is hardening rhythmically.

On the other hand, if large potentials are observed it is possible to infer that large stores of biological energy are being used and that, if the labour is prolonged, the patient will become exhausted sooner than a patient who is showing small potentials. Steer (1954) comes to much the same conclusion with regard to the smaller potentials which he records from two points close together. In fact the potentials which he records are ripples upon the larger waves which are recorded in our apparatus, and on occasions the records from our apparatus show ripples which are probably to be identified with waves demonstrated by the higher amplification of his apparatus.

Table II shows that there is no general relation between length of labour and the potential amplitude observed. This is not in agreement with Steer's statement (1954) but he, unfortunately, gives a diagram which shows only percentages of cases plotted against duration of labour, there being different diagrams for cases with small, medium and large potentials. We have attempted to reduce this diagram to a numerical table on the assumption that 60 per cent of his patients were primigravidae. The numbers obtained in this way depend upon the accuracy with which the percentages have been read off a small diagram and so are probably subject to a 5 to 10 per cent error. The result is shown in Table VI. It will be seen that there is

Table VI

Duration of Labour and Potential Amplitude (Steer)

Class	Large Potentials			Medium Potentials			Small Potentials			Totals
	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	Cases Noted	Cases Expected	χ^2	
>24H ..	3	4	0·2	17	33	8·0	31	13	25	51
24–6H ..	12	15	0·6	143	130	1·3	40	49	1·6	195
<6H	27	23	0·7	197	190	0·2	64	73	1·1	288

no systematic variation between the cases noted and the cases expected. The large potentials divide very much as expected: the medium potentials show a deficiency of cases for the over-24-hour class but the small potentials show a very large excess of cases for this class. Thus, although the χ^2 test for the table gives a value of 36, which is very high and indicates great significance for these deviations, the fact that there is no trend in the table leads to the same conclusion as in Table II, namely that there is more than one factor operating. One fact which gives rise to concern about Steer's diagram is the unusually high number of cases, 50 per cent of all observed, where the duration of labour was less than 6 hours.

Table III indicates that there is no obvious link between amplitude of potentials and the incidence of those excessively long labours which experienced full-time obstetricians had recorded as cases of inertia. Thus we are inclined to agree with Steer that inertia as a true clinical entity is of very infrequent occurrence, and that a good many cases which are classed as inertia are really cases of slow labour.

Clinical Thoughts on Slow Labour

Long and short labours may be analyzed irrespective of parity because the duration of the second and third stages is almost constant. The time variation is of course a first-stage matter, and prolonged labour is an aberration which covers almost exclusively the stage of cervical dilatation. It is necessary to contemplate this elementary truth, and the question arises as to why the primigravid varies so strikingly from the multigravid parturient. It has to be emphasized that the main effort is concerned with dilating the os up to a dilatation of 2 to 3 fingers diameter. The variable of first importance is not the total time of first and subsequent labours, but rather the time and work required to complete the first stage; and to be precise, the work—and perhaps the time—put into the operation of dilating the cervix up to the 2-finger mark.

It is generally agreed that the primipara performs more work (expenditure of biological resources) during the first stage than the multipara, and this is most obvious when primigravid and subsequent first stages in any particular individual are compared. Obstetricians explain the difference by analogy with the second stage and imagine that the primigravid cervix and related tissues are firmer, unstretched, and perhaps more rigid than in the multipara. While the existence of such a morphological difference is neither established nor disproved, its probability seems to us to be low. We wish to submit a simple hypothesis which offered itself in the early stages of enquiry into the functions under consideration. Let us consider a patient subject to inertia. She is usually a primipara, but occasionally a multipara.

The primigravida approaches term and begins to experience a few painful contractions. Her apprehension and uncertainty are sharpened and she is agog with anticipation. If uterine activity increases considerably, and particularly if unwonted spasms of pain accompany it, the woman imagines that she is in labour. Now if this process continues for the best part of the day, during which the patient feels that she has displayed great fortitude and calm in adopting a waiting attitude, she unhesitatingly goes to hospital that night. Labour may regress completely as it does when there is a false alarm, or an unproductive uterine activity with pain may persist for portions of the next day. This patient tends to be regarded as exhibiting inertia particularly if she has been in labour for some days. If on the contrary this parturient had been a multipara, she may well have felt the pains and been aware of the activity; but she would characteristically have ignored any thought that her time was at hand. She may also have experienced the discomfort of the hypothetical inertia subsequently, but she would have entered hospital only some days later and have been delivered not long after admission. The above sequence of events in the primipara may be an important basis of the morbid state called inertia. However, there arises the further question as to whether this is the only kind of inertia, or whether some cervices are more resistant to dilatation than others.

From our experience, particularly with parturition under tribal conditions in Africa, we are forced to the conclusion that an otherwise normal cervix may require much more than

average work to dilate it. In the most striking cases the fear complex was minimal. Furthermore, the number of obviously powerful contractions required to dilate the os beyond a diameter of 3 fingers was several times as many as the normal. Whether this type of cervix contains tissue which strongly resists stretching, or whether superior elasticity is responsible for abnormal shortening after stretching is not known.

We are at present investigating the variability of cervical resistance to dilatation. If it is possible to demonstrate significant rigidity of the cervix in subjects that suffer great prolongation of the first stage, the obstetrician will be forced to accept the concept of normal physical (? functional) rigidity—and we shall have a clear morphological type of inertia.

Steer's suggestion that true inertias are those which show no potential pattern at all is clearly opposed to the morphological conception of inherent cervical resistance. However, the practical difficulties of obtaining a clear decision are great because of the possibility, as stated by him and considered by us, that true inertias are only a few per cent of all cases which show excessively long first stages, and in the total series there are insufficient observations for a statistical demonstration. Thus the investigation of cervical resistance may be of considerable importance in the understanding of the phenomenon.

This work was carried out with the assistance of a donation from the University of the Witwatersrand and an annual research grant from the South African Council for Scientific and Industrial Research with whose permission this paper is published.

References

Dill, L. V., and Maiden, R. M. (1946): *Amer. J. Obstet. Gynec.*, **52**, 735.

Dill, L. V., and Maiden, R. M. (1948): *Amer. J. Obstet. Gynec.*, **56**, 213.

Halliday, E. C., and Heyns, O. S. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 309.

Lévy-Solal, E., Morin, P., and Zacouto, F. (1952): *Presse méd.*, **60**, 1335.

Reynolds, S. R. M. (1949): *Physiology of the uterus.* 2nd ed. Hoeber, New York.

Steer, C. M. (1954): *Amer. J. Obstet. Gynec.*, **68**, 867.

Steer, C. M., and Hertsch, G. J. (1950): *Amer. J. Obstet. Gynec.*, **59**, 25.

THE NATURAL HISTORY OF PELVIC TUBERCULOSIS

Being the Material Used for the Eighteenth William Blair-Bell Memorial Lecture

BY

TOM BARNS, M.A., D.M., M.R.C.O.G.

Consultant Gynaecologist, Johore, Malaya

(Formerly Research Fellow, Department of Obstetrics and Gynaecology, General Hospital, Newcastle-upon-Tyne)

THE natural history of infection with the tubercle bacillus varies in its course from one individual to another. According to the inherent resistance of the subject, the age, sex, and possibly other factors unknown to us, the disease may reveal itself as one or more of a variety of morbid states affecting the same or different organs. These manifestations can be grouped together under different headings according to the stage in the general infection at which they appear. Ranke (1917) has referred to three stages in tuberculosis; the primary or initial stage, the secondary or generalized stage, and the tertiary stage characterized by the development of tuberculous lesions in isolated organs.

Today the various types of tuberculosis are often described as primary or post-primary (Hedval, 1948), the primary phase corresponding to Ranke's stage one, and the post-primary phase to Ranke's stages two and three. It is the latter classification which will be used throughout this paper.

Disease of the pelvic organs is merely one of the manifestations resulting from invasion of the body by the tubercle bacillus, but the place of genital tuberculosis in the natural history of this invasion is not fully understood, nor has the route by which infection reaches the pelvic organs been fully investigated. The present study is an attempt to gain further insight into the pathogenesis of female genital tuberculosis and to integrate the aetiology of this condition with the wider problem of tuberculosis in general. Throughout the paper pelvic tuberculosis is regarded as a particular manifestation occurring during the course of generalized bodily disease, rather than as an isolated gynaecological entity.

PART I

THE MODE OF INVASION

Primary infection of the female genitalia by the tubercle bacillus is now generally accepted as being a condition of extreme rarity. In nearly all cases pelvic tuberculosis occurs as the result of endogenous spread of the disease from an established focus elsewhere in the body. Dissemination may take place by the blood stream from an extra-abdominal focus situated in the lung, glands of the neck, or elsewhere, or by blood stream, lymphatic, or direct local extension from a focus situated within the abdominal cavity. It is agreed that the lymphogenous route is probably rare as this would involve retrograde permeation of the lymphatic channels.

Many authorities have regarded the lung as the most important source of the infection and von Bardeleben (1912) maintained that genital tuberculosis was invariably a secondary manifestation of phthisis. Schlimpert (1911) and Horizontow (1911) both independently showed post-mortem evidence of pulmonary tuberculosis in 90 per cent of patients suffering from the genital lesion. Many of these cases, however, were also found to be suffering from tuberculous peritonitis, and Greenberg (1921) reported the incidence of this condition among his patients with pelvic tuberculosis to be 63 per cent and Berblinger (1946) 77 per cent. In such cases the abdominal lesion has been usually regarded as the focus from which the disease had spread to the pelvis. Since co-existent abdominal and pulmonary tuberculosis is present in many cases, each having been reported in more than half the patients suffering from a

lesion in the genital tract, one or other but not both must constitute the antecedent focus from which spread of the disease takes place into the pelvis, and doubt still persists regarding the relative frequency of responsibility of these various sites of origin. We do not yet know whether these foci are themselves primary tuberculous lesions, as in the case of a Ghon's focus, or subsequent manifestations as in the case of adult phthisis and tuberculous peritonitis. The human strain of tubercle bacillus was found in most of Jedberg's cases of pelvic tuberculosis (1950) and Liljedahl and Rydén (1950) have recently shown that 73 per cent of their patients had tuberculous lesions in the lung. Heynemann (1940) estimated 80 to 90 per cent of all cases as having pulmonary lesions, Puxeddu (1940) 78 per cent and Wegemer and Winkler (1941) 55 per cent. These recent reports are today generally regarded as proof of the pulmonary origin of the disease, although it should be noted that in all cases they come from Scandinavia or from other countries outside the British Isles, where epidemiological patterns of tuberculosis may differ considerably from those in this country particularly in regard to bovine infection; moreover in Great Britain at least it has been shown that the human strain bacillus can be isolated from 73 per cent of extra-pulmonary lesions (Medical Research Council, 1949).

In the course of this investigation special reference will be made to the nature, frequency and significance of co-existing manifestations of tuberculosis which are found in systems other than the genital tract in patients suffering from the pelvic lesion. The frequency of blood-spread invasion of the pelvic organs from the lung, compared with the frequency of transperitoneal spread from a focus in the abdomen, will be demonstrated; the primary character of such a focus of dissemination will also become apparent. At a later stage in the study (Part II), a relationship will be shown to exist between the time at which a patient receives her first infection with the tubercle bacillus, and the time at which dissemination takes place to the genital tract from the site of the primary tuberculous focus. A fundamental factor which appears to decide the predisposition of the genital tract to tuberculous infection will also be demonstrated: the relationship between the menarche and the time of exposure to the primary infection.

The Material and Its Method of Treatment

The basis of this study consists of 107 consecutive cases of genital tuberculosis attending the Gynaecological Department at the Newcastle General Hospital during the past 11 years. Laparotomy had been carried out in 55 of these cases in this department. There was therefore an excellent opportunity to obtain information concerning the presence of abdominal tuberculosis in these patients. In a further 25 patients a laparotomy had already been carried out before coming under observation; in 20 patients for appendicitis, and in 5 on account of unexplained abdominal pain. Uterine curettage was performed on one or more occasions in 83 patients of this series; 71 were curetted whilst this survey was in progress. Histological examination, biological examination and direct culture were carried out in all these cases and culture was also obtained from the spleen of the inoculated guinea pig in 27 cases.

Eighty-seven of the patients in this series were radiologically examined; a substantial number of former chest films of these patients were obtained from the records department of other hospitals to which they had been admitted in the past or from the files of the tuberculosis authorities. By this means we were able to receive evidence of post-primary pulmonary tuberculosis which was active at the time the patient was under our observation, confirmatory evidence of healed post-primary tuberculous lesions which had existed in the past, or evidence of a healed or active primary complex in the lung.

The most significant information, however, was obtained through the means of a careful anamnesis conducted on all these patients in order to obtain information about the date of the primary tuberculous infection, and its situation in the body. In the course of the anamnesis we sought and frequently obtained information concerning possible contacts undergone by the patient even when there was no significant incident recollected indicating that primary infection had taken place at the time of such

contact. The former addresses of all these patients were obtained and compared with the incidence of tuberculous infection reported from these houses and from neighbouring houses and this aspect of the study will be reported elsewhere. All events in the past histories have been verified by enquiries sent to the hospital or medical practitioner attending the patient at the time of reported illnesses, and no historical evidence has been accepted without such confirmatory evidence being obtained.

The information obtained from these investigations may be summarized as follows. (See Table I.)

(1) A past history of other forms of tuberculosis was obtained from 59 patients; 32 of these had had a pleural effusion, 22 had tuberculous peritonitis, 10 gave a history of erythema nodosum, and 5 of tuberculous cervical lymphadenitis. Seven others had sustained miscellaneous manifestations of tuberculosis.

TABLE I

Evidence of Tuberculosis in Other Systems, Among 67 Patients with Pelvic Tuberculosis

	No. of Cases
Evidence from the Medical History:	
Erythema nodosum	10
Pleural effusion	32
Tuberculous peritonitis	22
Tuberculous glands in neck	5
Tuberculous inguinal adenitis	1
Skeletal tuberculosis	3
Renal tuberculosis	1
Lupus	1
Mantoux conversion and serous meningitis associated with active primary lung tuberculosis	1
Evidence from Previous Laparotomies:	
Tuberculous glands in hernial sac	1
Abdominal tuberculosis	11
Evidence found at Laparotomy:	
Tuberculous peritonitis	13
Tuberculous peritonitis and calcified mesenteric glands	5
Calcified mesenteric glands	2
Radiological Evidence:	
Active primary complex	6
Healed primary complex	34
Active phthisis	1
Healed or doubtfully active phthisis	19
Calcified glands in the neck	3
Evidence from Renal Investigation:	
Renal tuberculosis	4

(2) The existence of abdominal tuberculosis had been noted in 11 patients at laparotomies in other hospitals; in another case tuberculous glands had been found in the inguinal sac during hernial repair. Among those who had had an appendicectomy, there had been abscess formation in 5, delayed union in 3, and fistula formation in another. Evidence of generalized tuberculous peritonitis was found at laparotomy in 18 cases; tuberculous peritonitis was associated with calcified mesenteric glands in 5 of these cases, and calcified mesenteric glands alone were found in 2 cases.

(3) Radiological investigation revealed a healed primary lung complex in 34 patients, of whom 15 had had a pleural effusion. Active adult phthisis was found in 1 patient, and radiological evidence of healed or doubtfully active phthisis in 19 patients, in none of whom had the lesion at any time been clinically manifest. Three patients were shown to have calcification of the cervical glands. The examination of previous X-rays showed an active primary tuberculous lung focus in 6 other cases.

(4) In 88 patients a full renal investigation was carried out, and of these 4 were found to have a tuberculous lesion in the kidney, otherwise symptomless.

(5) In 27 cases cultures of tubercle bacilli on Lowenstein-Jensen medium were obtained and these were all found to belong to the human strain with the exception of 1 case in which the culture was contaminated.

(6) Tuberculosis existing in systems other than the genital tract, whether in a healed or in an active state, was found by the above methods in 78 patients in all (73 per cent). If this estimate were to exclude those patients with a history of erythema nodosum or those with radiological evidence of primary tuberculous lesions in the lungs, there were then 67 patients in whom evidence of tuberculosis was found in other parts of the body (62 per cent). Of these the coexisting tuberculous lesion was active in only 8 patients (5 with renal tuberculosis; 1 with

active phthisis; and 2 with active tuberculous peritonitis).

Discussion

Four striking features are apparent from this evidence. In the first place, the high proportion of patients in whom other forms of tuberculosis were found (73 per cent). Secondly, the large number (32) of these patients who had had a pleural effusion (30 per cent). Thirdly, the large number (32) in whom tuberculous peritonitis was found (30 per cent) and, fourthly, the fact that all successful cultures of tubercle bacilli obtained were of the human strain.

The high incidence of other forms of tubercle among these patients emphasized the fact that genital tuberculosis is not an isolated gynaecological condition, but only one of the manifestations in a generalized systemic disease; it should be remembered, however, that active tuberculosis of other systems was only found in 8 patients. An incidence of other tuberculous manifestations has also been reported in patients suffering from pelvic tuberculosis by Clayton (1952), 36 per cent; Jedberg (1950), 56 per cent; Hagen (1947), 45 per cent; and Dietel (1943), 38 per cent.

The high incidence of pleural effusion among these women is consistent with the suggestion of Sibley (1950), based upon evidence obtained from the follow-up of patients suffering from pleurisy with effusion, that this condition represents a relatively serious phase of tuberculosis. A substantial proportion of the patients in whom the primary lesion is followed by pleurisy with effusion have been shown to develop evidence of haematogenous dissemination of the disease later on. Wegemer and Winkler (1941) report that 41 per cent of their patients with pelvic tuberculosis gave a past history of pleural effusion.

In 19 patients with no previous clinical manifestation of pulmonary tuberculosis, there was radiological evidence of healed or doubtfully active adult phthisis, suggesting either a high degree of host resistance in these patients or a low virulence of the infecting organism; either of these hypotheses is consistent with the chronic nature of the subsequent lesion in the pelvis.

It may be assumed that tuberculous pleural effusion, when it occurs up to the age of 20, is associated with an underlying active primary focus in the lung. It is clear that in the patients who gave such a history (24 cases), the disease had probably spread to the pelvis from this remote focus via the blood stream, as also in those others in whom there was radiological evidence of a healed or active primary focus in the lung (35 cases), in the glands of the neck (5 cases), or primary inguinal adenitis (1 case). These data refer to 52 cases in all.

In 5 other patients caseous or calcified glands were found in the mesentery and confirmed to be tuberculous in 2 cases. These, according to the views of Rich (1951), would represent true abdominal primary lesions, and from them the pelvis might subsequently have been infected by a process of contiguous extension or haematogenous spread. In 2 other patients mesenteric glands, seen at laparotomy, were said to be calcified; but an extra-abdominal focus was also found which suggested that these glands might not in fact have been tuberculous, for double primary infection is rare. It would thus appear that there were only 5 patients who showed evidence of primary abdominal tuberculosis. The true incidence of this type of infection, however, is probably higher than this would suggest when it is remembered that not all patients in this series underwent laparotomy.

Out of 57 cases, therefore (see Fig. 1), in whom evidence of the site of the primary lesion existed, the lesion was located in the lung in 80 per cent (46 cases), the glands of the neck in 9 per cent (5 cases), the abdomen in 9 per cent (5 cases) and the skin of the lower limb in 2 per cent (1 case). The fact that a human tubercle bacillus was isolated from the endometrium in 16 of these patients lends further support to the extra-abdominal site of the majority of these primary infections for the infecting organism in 65 per cent of all tuberculous abdominal lesions in this country has been shown to belong to the bovine strain (Medical Research Council, 1949).

Approximately one-third of the patients in this series had tuberculous peritonitis, and other authors have commented on this association; Berblinger (1946) found in 77 per cent of his patients evidence of previous peritoneal tuber-

culosis; Neu (1911) in 68 per cent; Greenberg (1921) in 63 per cent and Wetterdal (1925) in 57 per cent.

Now Haines (1952) has suggested that healed tuberculous peritonitis found in patients with pelvic tuberculosis represents a burnt out primary childhood infection with the bovine bacillus. This author maintains that subsequent genital involvement in these patients may have been caused by re-infection with the human type

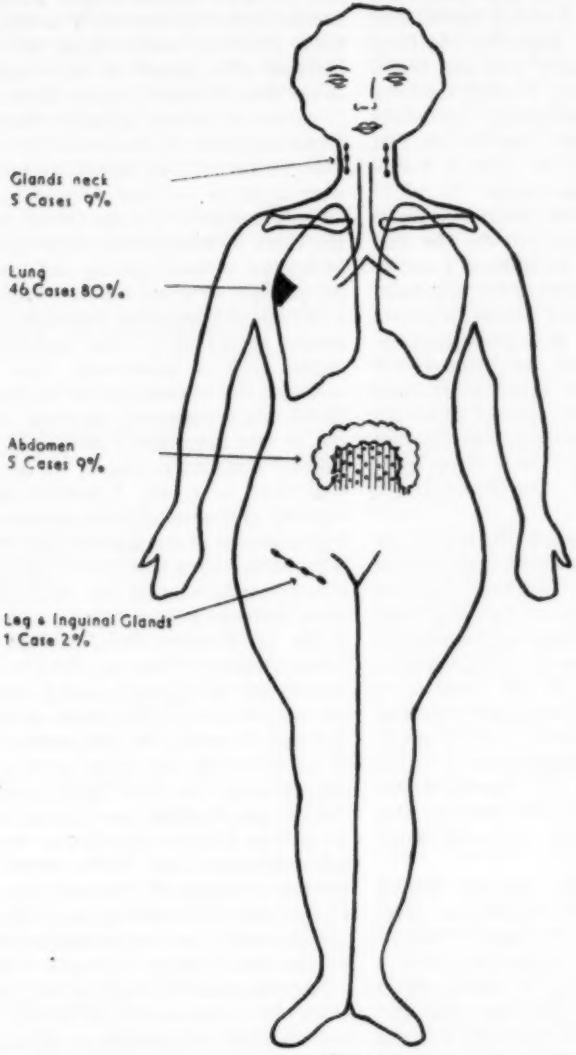


FIG. 1

Situation of the Primary Tuberculous Lesion in 57 Cases of Pelvic Tuberculosis.

bacillus taking place during adult life. Although "primary-like" lesions which are sometimes seen in later life are supposed to be caused by re-infection of a patient in whom sensitivity to tuberculo-protein has waned (Terplan, 1940), Haines's suggestion that this may occur as early as adolescence or early maturity appears unlikely. Tuberculous peritonitis is ordinarily caused by an underlying active primary complex in the abdomen, in the same way that a pleural effusion will result from an underlying primary focus in the lung; it may also be caused by the spill of infected material from any other source within the abdominal cavity, as for example a caseating tuberculous pyosalpinx. In the past the co-existence of tuberculous peritonitis and pelvic tuberculosis has been regarded as evidence that the pelvic infection arises by transperitoneal spread from an antecedent focus within the abdomen (Krönig, 1890; Albrecht, 1911). On the other hand the idea that tuberculous peritonitis may itself have arisen by the upward local extension of a pre-existing lesion in the pelvis originated many years ago in the writings of Mayo and Mayo (1912). Haines (1952) stated this sequence of events to be not unlikely, and Boyd (1947), stating the view of most general surgeons, believed this mechanism to account for the great majority of cases of female tuberculous peritonitis.

The latter possibility has gained support from the much higher incidence of tuberculous peritonitis among females after the age of puberty. Osler (1890), in his monograph on abdominal tuberculosis, stated that peritonitis is more prevalent among females and Mayo (1929) reported 195 patients with tuberculous peritonitis of whom 153 were females. Notifications of this condition in the city of Newcastle during the past 10 years also show preponderance among females over the age of 13, by 3 to 1. The weight of this argument is lessened, however, when we consider that the attack rate for all forms of extra-pulmonary tuberculosis after the age of 15 becomes considerably higher among females than among males of the same age groups (Daniels, 1952). In the Newcastle area the preponderance among females of all forms of extra-pulmonary tuberculosis is 1·6 to 1 (Newcastle-upon-Tyne, M.O.H., 1950).

Despite this objection, however, one cannot explain the high incidence (30 per cent) of patients suffering from tuberculous peritonitis in this series in terms other than that of a process involving local extension either in one direction or the other. The relatively avascular structure of the peritoneum makes simultaneous haematogenous dissemination both to peritoneum and pelvic organs an unlikely event, and post-mortems in cases of miliary tuberculosis seldom reveal involvement of the peritoneum in the otherwise generalized dissemination.

Thirty-two patients in the present series had tuberculous peritonitis; in 5 of these the typical glandular component of an abdominal primary lesion was identified at laparotomy. In 16 cases there was evidence, either from the history or from X-ray examination, of an extra-abdominal site of primary infection; a history of pleural effusion under the age of 20 or X-ray evidence of healed or active lung primary was demonstrated in 15 cases, and tuberculous glands of the neck in 1 case. We believe that in these latter cases, in which it is reasonable to assume the absence of primary abdominal tuberculosis, the genital tract had been involved by haematogenous spread from these distant extra-abdominal foci. Tuberculous peritonitis would therefore appear to have been secondary to the pelvic lesion in these patients, the peritoneum probably having become infected by the spill of tuberculous material from the Fallopian tubes. The isolation of a human type tubercle bacillus from 10 of these cases lends support to this explanation.

Thus the evidence in this series suggests that the peritoneum had been involved by upward extension from the genital tract in 76 per cent (16 cases) of the patients in whom the site of the primary focus could be identified. Transperitoneal spread of the infection from the abdomen to the pelvic structures could only have occurred in 14 per cent of these cases. Of the two forms of extension that take place, the upward dissemination of infected material would appear to be the commoner process. This observation is consistent with the higher incidence of tuberculous peritonitis among females, and also with the finding by Kahrs (1952) who, having demonstrated a preponder-

ance of males among those cases in which spread to the peritoneum had taken place from an abdominal primary focus, showed that the female patients in his series, who constituted the majority of the remaining cases of tuberculous peritonitis, were for the most part suffering from genital tract lesions.

PART II

The foregoing observations thus produce three very strong pieces of evidence leading to the conclusion that genital tuberculosis arises as the result of bacillaemia coming from a remote focus. In the first place, in 90 per cent of cases the known primary focus was extra-abdominal and in 80 per cent of cases that focus was in the lung. Secondly, we have indicated that there is strong evidence to support the view that, where tuberculous peritonitis was known to exist, it had resulted from upward extension of a pre-existing genital tract lesion. In the third place, in every case where the tubercle bacillus was typed, it was found to belong to the human strain, although in 65 per cent of cases of abdominal tuberculosis in this country the organism is known to be bovine (Medical Research Council, 1949).

Although bacillaemia has not so far been demonstrated in any patient suffering from genital tuberculosis, its existence in other forms of tuberculosis is now well established (Wilson, 1933; Boquet, 1935). Rich (1951) estimates that periods of bacteraemia occur in 90 to 95 per cent of all women suffering from chronic pulmonary tuberculosis. Debrés, Saenz and Broca (1934) and Rudback (1948) have demonstrated tuberculous bacilluria in children during the active period of a known primary complex. Choremis and Pantazis (1952) obtained positive bone marrow cultures from 16 out of 65 children, most of whom had an active primary complex at the time. There is increasing evidence that, when a fresh primary complex is present in the body, scattered tubercles, ordinarily few in number, can under normal conditions be found widely distributed among many organs. There is reason to believe that some of these lesions may remain quiescent for a considerable time although they contain viable bacilli, and that, during a period of lowered general resistance or of increased sensitivity of the individual organ, these foci may become active.

To quote from Rich (1951): "During the development of the primary lesion, bacilli ordinarily find their way into the blood stream whether directly from the pulmonary and lymph node lesions, or by passing through the sinusoids of the nodes and thence, by way of the thoracic duct, to the subclavian vein. In the great majority of cases the results of the bacillaemia are only sparsely scattered minute tubercles, which are eventually sterilized, and become hyalinized and absorbed. In some cases, however, viable bacilli persist in the lesions, and may later become reanimated and give rise to progressive disease of the organ in which they are situated, even though the primary lesions in the lung and regional lymph nodes remain completely arrested."

Where a hitherto unsuspected tuberculous endometritis is disclosed during investigation for infertility, it would thus appear possible that the lesion may have been present since shortly after the date of the primary infection. The time relation between the date of primary infection and the phase when dissemination takes place to the genital tract must now be considered.

Wallgren (1926) was the first systematically to investigate inter-relationships between the different manifestations of tuberculosis in the body, and was able to demonstrate a clearly defined chronological pattern correlating these various morbid states. An impressive series of reports has come from the Scandinavian countries, and to a lesser extent from Switzerland and France. In these, careful observations have been made and cases have been followed up over a period of many years from the time of development of the primary lesion. With few exceptions the later manifestations of tuberculosis are reported to occur during fairly regular time periods following the date of the initial infection. Thus the relationship between primary tuberculosis and erythema nodosum was analyzed by Wallgren (1926, 1929a); between primary tuberculosis and pleural effusion (Wallgren, 1929b); between primary tuberculosis and bone and joint infection (Wallgren, 1948); tuberculous meningitis (Wallgren and Nilsen, 1935); pulmonary tuberculosis (Wallgren, 1938); tuberculous peritonitis

(Wallgren and Lundblom, 1935); renal tuberculosis (Beskow, 1952), and suprarenal tuberculosis (Ustvedt, 1949).

Wallgren has shown that any of the primary infections may be accompanied by erythema nodosum whether such primary be in the skin, the naso-pharynx, the conjunctiva, the lung or the abdomen. In the majority of cases, however, the primary infection gives rise to no characteristic symptoms and passes unrecognized. An early post-primary phase characterized by a tendency to generalization occupies the next 3 months and during this stage the majority of cases of miliary tuberculosis and of tuberculous meningitis take place. A later post-primary phase extends over a period of a further 4 months, during which the majority of cases of pleural effusion and of ascitic peritonitis take place (see Fig. 2).

In the case of pleural effusion and tuberculous meningitis and peritonitis, when there is an underlying primary abdominal complex, these time relationships are sufficiently constant and closely defined to make it possible from a history of one of these manifestations to identify in retrospect to within a period of 1 to 12 months the time at which the primary lesion occurred. In the case of erythema nodosum the onset of this condition will coincide even more closely (within 1 to 6 weeks) with the time of primary infection.

These concepts have recently received further confirmation during the conduct of a survey on the epidemiology of childhood tuberculosis, which has been in progress in the Department of Child Health at Newcastle during the past years (Cammock and Miller, 1953).

In the present series there were 11 cases in whom exudative pleurisy or tuberculous peritonitis was preceded by overt manifestations of active primary tuberculosis, such as erythema nodosum, or radiological changes in the lung. Investigations of the time relationship between the primary and post-primary manifestation in these patients confirms that both pleural and peritoneal effusion took place in all cases within 12 months of the primary infection (see Table II).

In this study we have accepted as reliable evidence of the date of primary infection radiological evidence of an active primary lesion in lung (6 cases); a history of erythema nodosum (10 cases); of tuberculous glands in the neck (5 cases); or in the inguinal region (1 case); of observed Mantoux conversion (2 cases); and of pleural effusion at 20 years of age or less (24 cases). The details of 37 patients to which this evidence refers are summarized in Table III.

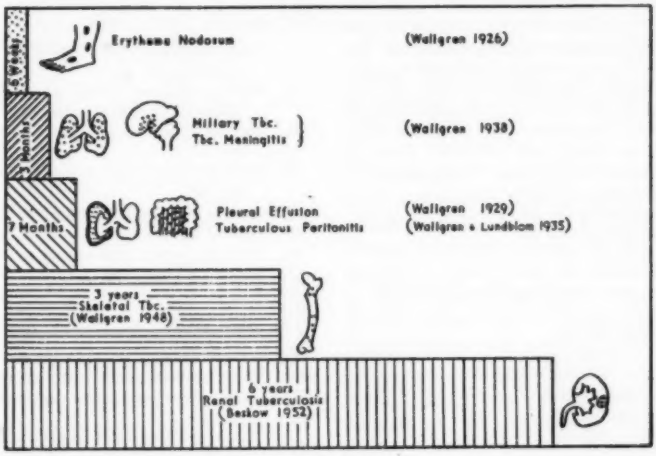


FIG. 2

Time-table of Tuberculous Infection.

TABLE II

The Time Relationship Between Primary and Post-primary Manifestation in Eleven Patients with Pleural Effusion or Tuberculous Peritonitis

Case No.	Age at Primary Manifestation	Age at Post-primary Manifestation
3	Active primary lung tuberculosis (X-ray): aet. 19 years 11 months.	Pleural effusion, aet. 19 years 9 months: simultaneously.
4	Erythema nodosum: aet. 17 years 3 months.	Pleural effusion: aet. 17 years 7 months: 4 months after primary.
5	Active primary lung tuberculosis (X-ray) and lymphocytic meningitis, Mantoux conversion 6 weeks later: aet. 15 years 2 months.	Pleural effusion: aet. 15 years 4 months: 6 weeks after primary.
22	Erythema nodosum: aet. 12 years 6 months.	Pleural effusion: aet. 13 years 6 months after primary.
38	Active primary lung tuberculosis (X-ray): aet. 16 years 5 months.	Pleural effusion: aet. 16 years 4 months: simultaneously.
60	Active primary lung tuberculosis (X-ray): aet. 14 years.	Pleural effusion: aet. 14 years: simultaneously.
66	Active primary lung tuberculosis (X-ray): and erythema nodosum: aet. 17 years.	Pleural effusion: aet. 17 years 10 months: 11 months after primary.
99	Erythema nodosum: aet. 20 years 4 months.	Pleural effusion: aet. 20 years 4 months: simultaneously.
8	Erythema nodosum: aet. 16 years 6 months.	Tuberculous peritonitis: aet. 17 years 6 months: 12 months after primary.
94	Erythema nodosum: aet. 32 years.	Tuberculous peritonitis: aet. 32 years 2 months: 2 months after primary.
17	Erythema nodosum: aet. 13 years 6 months (approximately).	Tuberculous peritonitis: aet. 14 years 6 months: approximately 12 months after primary.

TABLE III

The Evidence from which the Date of Primary Infection was Identified in 37 Patients with Pelvic Tuberculosis

Case No.	Evidence
99	Erythema nodosum and pleural effusion: aet. 20.
22	Erythema nodosum and pleural effusion: aet. 13.
4	Erythema nodosum and pleural effusion: aet. 17.
66	Erythema nodosum, aet. 16: pleural effusion, aet. 17: Mantoux conversion, aet. 16: X-ray active primary lung complex, aet. 16.
8	Erythema nodosum and history of contact: aet. 16.
92	Erythema nodosum: aet. 32.
45	Erythema nodosum: aet. 14.
17	Erythema nodosum: aet. 13.
27	Erythema nodosum: aet. 11.
95	Erythema nodosum: aet. 15.
73	X-ray evidence of active lung primary: aet. 14.
23	Pleural effusion: aet. 19.
59	Pleural effusion: aet. 20.
24	Pleural effusion: aet. 17.
55	Pleural effusion: aet. 15.
32	Pleural effusion: aet. 20.
72	Pleural effusion: aet. 17.
76	Pleural effusion: aet. 19.
87	Pleural effusion: aet. 12.
90	Pleural effusion: aet. 19.
94	Pleural effusion: aet. 19.
3	Pleural effusion and X-ray evidence of active lung primary: aet. 19.
5	Pleural effusion, X-ray active lung primary, and Mantoux conversion: aet. 15.
38	Pleural effusion and X-ray of active lung primary: aet. 16.
60	Pleural effusion and X-ray of active lung primary: aet. 14.
11	Pleural effusion and history of contact: aet. 17.
36	Pleural effusion and history of contact: aet. 17.
48	Pleural effusion and history of contact: aet. 13.
61	Pleural effusion and history of contact: aet. 15.
74	Pleural effusion and history of contact: aet. 20.
84	Pleural effusion and history of contact: aet. 11.
18	Tuberculous cervical lymphadenitis: aet. 14.
62	Tuberculous cervical lymphadenitis: aet. 9.
69	Tuberculous cervical lymphadenitis: aet. 17.
103	Tuberculous cervical lymphadenitis: aet. 12 months.
39	Tuberculous cervical lymphadenitis and history of contact: aet. 22.
2	Tuberculous inguinal lymphadenitis and history of contact: aet. 22.

In 19 cases it was considered that there was insufficient evidence from which to deduce the date of primary infections. In 1 patient, who had facial lupus at the age of 13, no evidence of a gland component had been recorded at the time of the illness. In 8 cases of pleural effusion, occurring between the ages of 20 and 30, there was no proof that these were not secondary to adult phthisis. In 10 cases there was a history of tuberculous peritonitis with or without evidence of an abdominal primary and it is possible that, in these cases, peritonitis resulted from upward extension from a pre-existing pelvic focus. In a further group of cases there was a clearly defined history of limited intimate exposure to tuberculous infection, but there was no history of primary or early post-primary manifestation. By adopting these strict criteria, it is probable that several genuine examples of primary infection have been overlooked.

Among the 37 cases, in which there was evidence of the time of primary infection, there were only 24 per cent in which the histological diagnosis of pelvic tuberculosis was made within 5 years of the date of the primary (Table IV).

TABLE IV

Showing the Proportion of Patients in whom (i) *the Diagnosis of Pelvic Tuberculosis was Made and* (ii) *the Onset of Clinical Disturbance Due to this Condition Occurred, During Varying Time Periods Following the Date of Primary Tuberculous Infection*

Time Periods after Primary Infection	0–1 year	1–3 years	3–5 years	5–9 years	9–15 years
Proportion of cases diagnosed (per cent)	8	2	14	30	29
Proportion of cases in whom the first onset of symptoms occurred (per cent) ..	30	26	19	14	8

It was realized however that among these cases there were many in whom the infection was latent in the pelvis (42 per cent) and may have remained hidden for many years before diagnosis was achieved. Generally speaking the only complaint in this type of case was of primary infertility and this was not regarded as being a valid symptom until at least 3 years had elapsed. In certain other cases it was possible to obtain a retrospective history of other symptoms such as menorrhagia, amenorrhoea, or abdominal pain. When the date of the first clinical manifestations of the disease, including that of infertility, was considered in this way it was found that in 75 per cent of the patients, in whom the date of the primary could be identified, the onset of symptoms had occurred within 5 years of this infection, in 56 per cent within 3 years and in 30 per cent within 12 months of the estimated date of the primary infection (see Table IV). Moreover, when considering these findings it should be borne in mind that, because of the recognized chronicity of pelvic lesions, it is possible that there may have been many cases in which tuberculous infection first invaded the pelvis even sometime before clinical disturbance was manifest.

Now there is considerable evidence that intermittent bacillaemia accompanies the period of activity of primary tuberculous lesions (vide supra). In most cases, because the primary lesion is healed within 12 months of its initiation, bacillaemia and its attendant risk of dissemination ceases after this time (Wallgren, 1948). Thus post-primary manifestations would be expected to result from dissemination taking place within 12 months of the initial infection. The time relationships which have been demonstrated between the date of primary infection and the onset of first clinical disturbance due to genital tract infection are thus consistent with the conclusion that invasion of the pelvic organs occurs soon after the patient received her primary infection.

Although in the majority of cases (56 per cent) the onset of clinical disturbance is to be expected within 3 years or so of this event, many cases remain in whom symptoms are not sufficiently marked to lead to the recognition of the disease at this early stage. Table IV, which demonstrated these time relationships however, includes many patients in whom the onset of symptoms, and the establishment of the histological diagnosis, took place within only 12 months of the patients having received their primary infecting dose of tubercle bacilli.

Winkler and Wegemer (1940) state that tuberculous salpingitis is manifest most often

within 5 years of a pleural effusion. Hagen (1947) demonstrated that one-third of his cases of genital tuberculosis showed their first symptom within 1 year, and two-thirds within 5 years of pleural effusion, and Jedberg (1950), in a recent survey of 186 cases of pelvic tuberculosis, found that 20 per cent of his patients developed their first symptom within the year and two-thirds within 5 years of the initial manifestation of the disease. It must be noted that Jedberg's cases include many which were rejected from this series as not being necessarily primary manifestations.

The findings reported by the above authors are in agreement with those in the present series which suggest that pelvic invasion probably takes place during the early post-primary phase of the infection. The onset of symptoms in female genital tuberculosis can therefore be expected to begin within 3 years of the primary infection in the majority of cases and it is suggested that, at whatever time in life the diagnosis of pelvic tuberculosis is made, the disease has probably been present in the genital tract since before the time at which healing of the primary lesion occurred.

These conclusions are convincingly illustrated in the following case histories:

Case No. 5

Age 13	Menarche.	
Age 14$\frac{3}{12}$	Mass X-ray on leaving school:	no lesion seen in chest.
Age 14$\frac{1}{2}$	Conception.	
Age 15	10th week of pregnancy:	benign lymphocytic meningitis (Green's active primary lesion in chest), syndrome. Mantoux negative.
	16th week of pregnancy:	Pleural effusion. Mantoux positive.
	29th week of pregnancy:	Ante-partum haemorrhage, premature onset of labour; fresh stillbirth; post-mortem examination; normal foetus.
	9 weeks after delivery:	Mass palpated in right Fallopian tube. Biopsy—*Tbc. cervicitis, Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis within 6 months of primary infection.

Case No. 8

Age 12	Menarche.
Age 16	Exposure to pulmonary tuberculosis contact. Erythema nodosum.
Age 17	Tuberculous peritonitis. Mantoux positive. Onset of mittelschmerz and irregular menstruation.
Age 21	Sought medical advice complaining of above symptoms. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis 5 years after primary infection. Onset of symptoms one year after primary infection.

Case No. 16

Age 14	Menarche.
Age 19	Marriage. Intimate exposure to tuberculous infection.
Age 24	Right pleural effusion. Onset of bloodstained vaginal discharge and heavy irregular episodes of uterine bleeding.
Age 25	Histological diagnosis of *Tbc. endometritis* and *Tbc. cervicitis.* Chest X-ray: healed primary complex, right lung.

Conclusion: Histological diagnosis of pelvic tuberculosis within 12 months of probable primary lung infection.

Case No. 66

Age 14	Menarche.
Age 16	Erythema nodosum. Active primary lesion in chest.
Age 17	4th month following erythema nodosum: Mantoux test negative.
Age 17	Mantoux test positive.
Age 17	Left pleural effusion. Onset of irregular episodes of bleeding.
Age 17	Unilateral tubovarian mass. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Histological diagnosis of pelvic tuberculosis one year after primary infection.

Case No. 3

Age 16	Menarche.
Age 19	Left pleural effusion: active primary lesion in chest. Marriage during same year.
Age 20	Tbc. peritonitis.
Age 21	Routine infertility investigations. Histological diagnosis of *Tbc. endometritis.*

Conclusion: Diagnosis of pelvic tuberculosis within 2 years of primary infection.

A further interesting observation emerges from the study of the ages at which primary tuberculous infection took place in the 37 patients in this series.

Table V shows that in the majority of cases primary tuberculous infection had occurred late in life, coinciding in most patients with the period of adolescence or early maturity.

When the time interval elapsing between the patient's age at the menarche and her age at

TABLE V

Age at the Time of Primary Tuberculous Infection in 37 Cases of Pelvic Tuberculosis

Age at Primary Infection	0–4 years	5–9 years	10–14 years	15–19 years	20–24 years	24 and over
Number of Patients ..	1	1	10	18	6	1

the time of primary tuberculous infection was estimated in each of these 37 cases, it was found that in 46 per cent the primary lesion was established within 2 years of the menarche, and in 70 per cent within 4 years of this event (see Table VI).

TABLE VI

Showing the Association Between the Age of Individual Patients at the Time of Their Primary Infection and Their Age at the Menarche

Length of Time Interval Between Menarche and Primary Infection	Number of Cases	Percentage
Primary infection occurring during same year as menarche	3	8·1
Primary infection within 2 years of the menarche	17	46
Primary infection within 4 years of the menarche	26	70
Primary infection within 6 years of the menarche	31	85
Primary infection occurring within longer than 6 years after the time of the menarche	37	100

The report on the Prophit survey (Daniels *et al.*, 1948) showed that 63 per cent of the young adult group in this country (1935 to 1944), aged 15 to 16, had already received their primary infection; the recent survey by the Medical Research Council (1952) showed that 55 per cent of girls in the urban areas in the North of England including Tyneside had undergone Mantoux conversion by the age of 15.

The remarkable fact has therefore been demonstrated that in the patients in this series who were suffering from genital tract tuberculosis, the age distribution of tuberculous primary infection is directly contrary to the normally expected age distribution for this event among people living in the Newcastle-upon-Tyne area.

If the majority of individuals living in Newcastle receive their primary tuberculous infection during childhood, and if, as we have shown in this study, genital tuberculosis is an early post-primary manifestation of the general invasion of the body by the tubercle bacillus in which the majority of patients may be expected to manifest their first symptom within 3 years of this event, then it is to be expected that pelvic tuberculosis would be diagnosed among children in this area.

A search made of the clinical records of the gynaecological department at the Newcastle General Hospital, and of the records of the department of child health at the Royal Victoria Infirmary during the previous decade, 1942–1951, failed to discover a single female patient under the age of 12 years having been admitted to either unit with a diagnosis of genital tract tuberculosis.

This search was extended to the post-mortem records of all female children dying under the age of 12 years during this 10-year period. Five hundred and sixty-two autopsy reports were examined in this way, many on children who had died from tuberculous meningitis, a bacillaemic form of tuberculosis. Only one case was found, a child dying from miliary tuberculosis, in whom a tuberculous lesion was identified in the genital organs; this child, however, who died at 10 years of age, may be said already to have been approaching the adolescent period of life.

An examination of the literature by Kelly in 1901 showed only 20 cases of genital tuberculosis to have been reported in children up to that date.

Thus it appears that, when primary tuberculous infection occurs during childhood, there is little or no risk of subsequent dissemination to the genital tract taking place. When primary infection and post-primary tuberculous bacillaemia coincide with the period of adolescence or early maturity, however, there would appear to exist at this time a special vulnerability of the female genital tract to invasion by the tubercle bacillus.

If confirmation of these findings is forthcoming from other centres, there would appear

to be grounds for suggesting that those girls who are Mantoux negative by the time they reach the age of 11 should be rendered positive by B.C.G. inoculation. Tuberculous meningitis, which is a particular risk accompanying primary infection in early childhood, has been reduced or almost eliminated in Scandinavia by the adoption of B.C.G. inoculation; genital tuberculosis, which results in sterility, appears to be the particular risk of primary infection in adolescence, and this might also be reduced or eliminated by taking similar steps.

Summary

(1) The mode of invasion of the genital tract in 107 women suffering from pelvic tuberculosis has been investigated.

(2) A high proportion of patients (73 per cent) showed evidence of other forms of tuberculosis; pleural effusion and tuberculous peritonitis each occurring in approximately one-third of the cases. In only 8 patients were these co-existing lesions still in an active state.

(3) The primary site of tuberculous infection was located in 57 patients; this was found to have been in the lung in 46; in the glands of the neck in 5; in the abdomen in 5; and on the skin in 1 case. This suggests that invasion of the pelvis had taken place by the haematogenous route in at least 52 (90 per cent) of these patients.

(4) Evidence of the site of the primary was available in 20 patients who had had tuberculous peritonitis. In only 1 out of every 4 of these cases was the site of this primary within the abdomen. It would therefore appear probable that peritonitis had arisen in at least 75 per cent of these patients as the result of spread of infected material from a pre-existing tuberculous focus in the pelvis.

(5) The infecting organism was found to belong to the human strain tubercle bacillus in all cases in which culture was successful.

(6) The date of the primary infection was identified in 37 patients. A relationship has been shown to exist between the time at which the patient receives her first infection, and the time at which the infection proceeds to invade the genital tract from this primary source. In many cases it is only a matter of a few months before the invasion occurs; in more than half of the patients (56 per cent) there was evidence that pelvic infection had taken place within 3 years of the primary. From this evidence it is believed that dissemination to the pelvis probably takes place during the period of activity of primary tuberculous lesions.

(7) Genital tuberculosis is shown to be a particular risk accompanying primary tuberculous infection during adolescence. It has been suggested that this should provide additional grounds for urging that girls be rendered tuberculin positive by B.C.G. inoculation before reaching this age.

I wish to acknowledge the close collaboration given to me in the conduct of these investigations and in the preparation of this paper by Mr. Linton M. Snaith, M.D., M.S., F.R.C.S., F.R.C.O.G., who put at my disposal the clinical material which has been used in these studies.

Bibliography

Albrecht, H. (1911): *Dtsch. Kongr. Gynäk. Geburtsh.* (quoted by Norris, C. C. (1931)).

von Bardeleben, H. (1912): *Lancet*, **1**, 1751.

Berblinger, W. (1946): *Schweiz. med. Wschr.*, **76**, 1223.

Beskow, A. (1952): *Acta tuberc. scand.*, Suppl. 31.

Boquet, A. (1935): *Rev. Immunol., Paris*, **1**, 186.

Boyd, W. (1947): *Surgical Pathology*. 6th ed. Saunders, Philadelphia.

Cammock, R., and Miller, F. J. W. (1953): Personal communication.

Choremis, C., and Pantazis, S. (1952): *Lancet*, **1**, 748.

Clayton, S. G. (1952): *Brit. J. Tuberc.*, **46**, 103.

Daniels, M. (1952): *Proc. R. Soc. Med.*, **45**, 11.

Daniels, M., Ridehalth, F., Springett, V. H., and Hall, I. M. (1948): *Tuberculosis in young adults. Report on the Prophit Survey*. Lewis, London.

Debrés, R., Saenz, A., and Broca, R. (1934): *Bull. Soc. méd. Hóp. Paris*, **50**, 771.

Dietel, H. (1943): *in* Seitz and Amreich: *Biologie und Pathologie des Weibes*. Vienna, **5**, 108.

Greenberg, J. P. (1921): *Johns Hopk. Hosp. Rep.*, **21**, 97.

Hagen, O. (1947): *Nord. Med.*, **36**, 2197.

Haines, M. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 721.

Hedval, E. (1948): *Forelasningar i tuberkulos*. Stockholm (quoted by Jedberg, H. (1950)).

Heynemann, T. (1940): *Geburtsh. Frauenheilk.*, **2**, 336.

Horizontow, M. I. (1911): *Zbl. Gynäk.*, **35**, 1731 (quoted by von Bardeleben, H. (1912)).

Jedberg, H. (1950): *Acta obstet. gynec. scand.*, **31**, Suppl. 1.

Kahrs, T. (1952): *Tubercle*, **33**, 132.

Kelly, P. (1901): *Johns Hopk. Hosp. Rep.*, **2**, 201.

Kronig, G. (1890): *Cbl. Chir.* (quoted by Norris, C. C. (1931)).
Liljedahl, S. O., and Rydén, A. B. V. (1950): *Acta obstet. gynec. scand.*, **30**, 359.
Mayo, C. H. (1929): *Ann. Surg.*, **90**, 614.
Mayo, C. H., and Mayo, M. I. (1912): *A collection of papers*. Saunders, Philadelphia.
Medical Research Council (1949): *J. Hyg., Camb.*, **47**, 337.
Medical Research Council (1952): *Lancet*, **1**, 775.
Neu, M. (1911): *Med. Klinik.*, **32**, 1323 (quoted in Greenberg, J. P. (1921)).
Newcastle-upon-Tyne, Medical Officer of Health (1950): *Annual report*.
Norris, C. C. (1931): *Gynecological and obstetrical tuberculosis*. Appleton, New York.
Osler, W. (1890): *Johns Hopk. Hosp. Rep.*, **2**, 67.
Puxeddu, E. (1940): *Riv. ital. Ginec.*, **23**, 211 (abstr.: *Int. Abstr. Surg.*, 1940, **71**, 144).
Ranke, E. (1917): *Münch. med. Wschr.*, **64**, 305.
Rich, A. R. (1951): *The pathogenesis of tuberculosis*. Blackwell, Oxford.
Rudback, L. (1948): *Nord. Med.*, **40**, 2222.
Schlimpert, H. (1911): *Arch. Gynäk.*, **94**, 863 (quoted by von Bardeleben, H. (1912)).
Sibley, J. C. (1950): *Amer. Rev. Tuberc.*, **62**, 314.
Terplan, K. (1940): *Amer. Rev. Tuberc.*, **42**, Suppl. 2.
Ustvedt, H. J. (1949): *Acta tuberc. scand.*, Suppl. 21, 102.
Wallgren, A. (1926): *Acta med. scand.*, **16**, Suppl. 1, 363.
Wallgren, A. (1929a): *Rev. franç. Pédiat.*, **5**, 749.
Wallgren, A. (1929b): *Amer. J. Dis. Child.*, **38**, 829.
Wallgren, A. (1938): *Lancet*, **1**, 417.
Wallgren, A. (1948): *Tubercle*, **29**, 245.
Wallgren, A., and Lundblom, A. (1935): *Nord. med. Tidskr.*, **10**, 1699 (quoted by Jedberg, H. (1950)).
Wallgren, A., and Nilsen, T. (1935): *Rev. franç. Pédiat.*, **11**, 37.
Wegemer, E., and Winkler, H. (1941): *Dtsch. Tuberkbl.*, **15**, 109.
Wetterdal, P. (1925): *Acta gynec. scand.*, **3**, 169.
Wilson, G. S. (1933): *Spec. rep. Med. Res. Counc.*, **182**.
Winkler, H., and Wegemer, E. (1940): *Zbl. Gynäk.*, **64**, 1961 (abstr.: *Yearb. Obstet. Gynec.* Chicago, 1940).

RADIUM MENOPAUSE OR HYSTERECTOMY

Part I—The Effects of the Radiation Menopause—A Controlled Study

BY

A. C. TURNBULL, M.B., M.R.C.O.G.

Registrar

Gynaecological Unit, Aberdeen Royal Infirmary

FOR many years much adverse criticism has been directed at the practice of inducing the menopause by radium or X-rays to cure functional uterine haemorrhage. It is said that the symptoms which result, such as flushing and sweating, are much worse than those which would occur naturally (McLaren, 1941). In many cases the treatment is said to be followed by a sudden loss of sexual desire, and changes are produced in the genital tract which are held to cause dyspareunia (McLaren, 1950). Furthermore, it has been suggested by Corscaden, Fertig and Gusberg (1946), and by Speert and Peightal (1949) in particular, that the liability to malignant disease in the body of the uterus is increased.

Where conservative treatment is unsuccessful, the alternative to radiation is hysterectomy, which despite a higher operative mortality has become increasingly popular because it appears to avoid the disadvantages attributed to induction of the menopause. Cancer cannot develop later, either in the body of the uterus or in the cervix if, as is usual nowadays, total hysterectomy is performed. Furthermore, if some ovarian tissue is conserved, a natural menopause will be experienced in due course with, it is argued, relatively mild symptoms.

Nevertheless, induction of the menopause by radiation has often been preferred to hysterectomy in the Gynaecological Department of Aberdeen Royal Infirmary in women over 40 years of age, because it is safer than hysterectomy, especially in "poor-risk" cases, and has been found simple and effective.

It was felt that the value of this policy should be carefully assessed. This paper deals with one aspect of this enquiry, namely the question of how the symptoms which develop after the radiation menopause compare with those after the natural menopause.

The incidence of symptoms following the menopause has been assessed by many workers, generally using the degree of flushing and sweating as an index of the amount of disturbance. Published reports of symptoms after the natural menopause show great variation in incidence: Barrett (1938), 20 per cent; the Council of the Medical Women's Federation (1933), 62·5 per cent; Werner (1938), 91·6 per cent. Similar variations are seen in the incidence of symptoms in cases where the menopause is induced by radiation: Hunter (1939), 10 per cent; Malpas (1937), 23 per cent; Schmitze and Towne (1947), 48 per cent.

These reports deal with either the natural or the artificial menopause but none of them attempt to compare or contrast the symptoms in the two types. Such a study should, if possible, be done by one person and the groups should be comparable in every respect except in the way the menopause occurred. McLaren (1941) has carried out such a study and found that 17 per cent of women having a natural menopause and 44 per cent having an induced menopause had moderate or severe flushing. A scrutiny of his paper shows, however, that great differences existed in the time that elapsed between the time of the occurrence of the menopause and the interview. The average age at interview of the treated cases was 45 and of the controls 63. In the treated cases the interval between treatment and interview is stated to be not less than 1 year and, although exact times are not given, it is clear that in most the interval was short. In the control group the time interval must have

averaged about 18 years and in some cases much longer, for the oldest patient was 88 years of age and several were over 70. In a second paper McLaren (1950) reports a very similar incidence of severe flushing (49 per cent) in a series of 118 cases after an average interval of 2 years from the time of treatment, but there were no controls. It is obvious that the control group in the first paper cannot be regarded as satisfactory since it is most unlikely that women of 65 or 70 recall with any degree of reliability the severity of their menopausal symptoms.

McLaren (1950) also reported that, after the radium menopause, 52 per cent of cases in whom desire was previously normal noticed that the sexual urge was reduced or lost, while 10 per cent of his cases had developed dyspareunia. As control cases were not examined in this investigation, he was unable to say how these figures compared with what happened naturally.

In this investigation, the findings in a group of women who had the menopause induced by radiation have been compared with those in another group who experienced a natural menopause. The incidence and severity of flushing, sweating, emotional instability, alteration in sexual desire, dyspareunia and vaginal discharge have been studied.

Material

In all, 157 cases were studied, 101 who had the menopause induced (97 by radium and 4 by X-rays) and 56 who had experienced a natural menopause. The treated cases represent a consecutive series of women admitted to the Aberdeen Royal Infirmary and subsequently traced successfully. The radium dosage was 2,400 mg.-hours. With X-rays a total of 600 r. was given in 3 treatments. The controls were obtained in two ways: (*a*) 28 women in whom curettage alone had been performed in the Gynaecological Department for irregular bleeding near the menopause and in whom the menopause had come on some time later without further treatment being necessary; and (*b*) 28 volunteers from local women's organizations. In none of the control cases was the interval between the menopause and the investigation more than 10 years, and in most it was a great deal less.

The use of the volunteer in any research of this kind raises the formidable problem of selection, but no other method of obtaining a sufficient number of suitable control cases could be devised. There is, however, no reason to believe that this invalidates the findings. An attempt to find control cases in surgical wards as MacLaren did was most unsatisfactory, since most of the women available were too old, as in McLaren's series.

Interval from Menopause to Interview

In Table I it is seen that all the treated cases and 84 per cent of the controls were investigated within 6 years of the menopause. While 16 per cent of the controls were seen 7 to 10 years after the menopause, the average interval in the two groups is almost identical.

Age at Menopause

Table II shows that 40 per cent of the treated cases and 20 per cent of the controls have had the menopause before 45 years. In the only control case where the menopause occurred before the age of 40 years menstruation ceased after an abortion at 36 years of age, and typical menopausal symptoms developed soon afterwards.

Table I

Distribution of Interval between Menopause and Interview
(Percentages in brackets)

	Total	Interval (Years)					
		1–2	3–4	5–6	7–8	9–10	Average
Radiation cases ..	101	27 (26·7)	49 (48·5)	25 (24·8)			3·6 years
Control cases ..	56	22 (39·3)	15 (26·4)	10 (17·8)	6 (10·7)	3 (5·4)	3·8 years

Parity

The distribution of parities in the two groups is very similar. Fourteen (13·9 per cent) of the treated cases and 6 (10·7 per cent) of the controls were nulliparae. In the treated group, 29 (28·7 per cent) had 1 or 2 children, and 55 (54·5 per cent) had 3 or more. The comparable figures in the control group were 14 (25 per cent) and 34 (60·7 per cent) respectively. In 5 cases, 3 treated and 2 controls, details of parity were incomplete.

Marital Status

The marital status of patients at the time of investigation was also similar in each group. Of the treated cases 79 (78·3 per cent) were married, 9 (8·9 per cent) single, 10 (9·9 per cent) widowed, and 3 (2·9 per cent) separated from their husbands. Of the control cases, 48 (85·8 per cent) were married, 4 (7·1 per cent) single, 3 (5·3 per cent) widowed, and 1 (1·8 per cent) divorced.

Method

Each patient was interviewed personally in a session lasting for 1½ to 2 hours. While a set plan could not be rigidly adhered to, as patience and tact had to be exercised, every attempt was made to cover the same ground thoroughly and systematically in each case. Special charts were used, and the severity of each symptom was graded on a pre-determined scale. Leading questions were avoided as far as possible, but, when they had to be used, every effort was made to frame them in such a way as to avoid influencing the answers. The technique of interviewing patients used was obviously of great importance, and advice was sought from Professor Millar of the Department of Mental Health and his staff. They were kind enough to observe by the "one-way" screen the interviewing of 9 patients and then personally conducted the interviews with 3 patients. Observation of their technique and the adoption of suggestions they made proved invaluable.

In all the treated cases, and in the majority of controls, general physical and pelvic examination was carried out.

Findings

The most disturbing symptoms, flushing, sweating and emotional disturbances, cannot be measured objectively or precisely. Organic changes, such as stenosis of the vagina or thinning of its epithelium, can be observed and measured with some accuracy, but usually pass unnoticed by the patient unless they give rise to symptoms such as dyspareunia, pruritus, or vaginal discharge, which must, to a considerable extent, be assessed subjectively. In this investigation much more emphasis has been placed on assessing the symptomatic effects of the menopause than on measuring organic changes.

Flushing and Sweating

The severity of flushing both before and after the menopause was assessed and in the case of the latter graded not only at the time of the interview but also when it was at its worst. Flushing was assessed as absent, mild, moderate or severe, and the criteria used were the same as those employed by McLaren to allow of an accurate comparison with his findings.

Table III shows that nearly half of the treated and the control cases had flushings before the cessation of menstruation, the more severe forms being slightly more common in the cases subsequently treated, 23·7 compared to 17·7 per cent.

Table IV shows that after the menopause

Table II

Distribution of Age at Menopause
(Percentages in brackets)

	Total	Under 40	40–44	45–49	50–54	55+
Radiation cases ..	101	5 (4·9)	37 (36·8)	41 (40·6)	16 (15·8)	2 (1·9)
Control cases ..	56	1 (1·8)	11 (19·6)	32 (57·1)	10 (17·9)	2 (3·6)

TABLE III

Distribution of Pre-menopausal Flushing
(Percentages in brackets)

	Total	None	Severity of Flushing			Not Graded
			Mild	Moderate	Severe	
Radiation cases ..	101	57 (56·5)	20 (19·8)	22 (21·8)	2 (1·9)	—
Control cases ..	56	31 (55·6)	14 (25)	9 (16)	1 (1·7)	1 (1·7)

TABLE IV

Distribution of Post-menopausal Flushing

	Total	Severity at Worst					Severity at Interview				
		None	Mild	Mod-erate	Severe	Not Graded	None	Mild	Mod-erate	Severe	Not Graded
Radiation cases ..	101	14	40	32	15	—	45	34	18	1	3
Per cent		13·9	39·6	31·7	14·8		44·6	33·7	17·9	0·9	2·9
Control cases	56	19	13	17	6	1	30	12	10	2	2
Per cent		33·9	23·2	30·4	10·7	1·8	53·6	21·6	17·8	3·5	3·5

there was an increase in the incidence of flushing in both groups. When symptoms were worst, 87 (86 per cent) of the treated cases and 36 (64 per cent) of the controls were affected, although the numbers had fallen to 53 (52·5 per cent) and 24 (42·9 per cent) respectively when the patients were interviewed. A higher incidence of mild flushing in the treated cases largely accounts for the overall difference in the incidence for moderate or severe flushing developed in 47 (46·5 per cent) of treated cases and in 23 (41 per cent) of the controls. The incidence in treated cases is much the same as that found by McLaren, who reported that 43·6 per cent of his patients experienced moderate or severe flushing after the radium menopause; and by Schmitze and Towne (1947) who stated that 48 per cent of cases developed "serious menopausal manifestations" after radiation. The close approximation of the findings suggests, in fact, that similar methods of interviewing patients and of grading symptoms must have been adopted in each of these investigations, and that the amount of upset can be assessed fairly accurately.

The great similarity of the incidence of severe flushings in treated cases in this paper with those in McLaren's series suggests that the doubts raised earlier about the suitability of the control cases in McLaren's series is justifiable. Table IV shows that in this series even by the time of the interview the number of patients who complained of severe flushing was less than half what it had been when the symptoms were at their worst. It seems clear that the severity of flushing after the induced or natural menopause is about the same.

Predisposition to Flushing

An attempt was made to find out whether any factors were related to the severity of the flushing. The following were investigated:

(a) *Age at Menopause.* One case was excluded from the control group because of incomplete information about pre-menopausal flushing. Because of the small total number of cases they were grouped into three categories, 44 years or less, 45 to 49, and 50 years or more. Cases with mild or no flushing and those with severe or moderate flushing were grouped together. The severity of post-menopausal flushing was assessed when the symptom was at its worst.

TABLE V

The Relationship between Age at Menopause and the Severity of Flushing Before and After the Menopause
(Percentages in brackets)

	Age at Menopause	Severity of Flushing				Total
		Before the Menopause		After the Menopause (At Worst)		
		Absent or Mild	Moderate or Severe	Absent or Mild	Moderate or Severe	
Radiation Cases	44 years or less ..	35 (83)	7 (17)	21 (50)	21 (50)	42
	45–49	28 (67)	13 (33)	22 (53)	19 (47)	41
	50 and over ..	14 (80)	4 (20)	11 (60)	7 (40)	18
	Total	77	24	54	47	101
Control Cases	44 years or less ..	10 (83)	2 (17)	6 (50)	6 (50)	12
	45–49	25 (81)	6 (19)	18 (58)	13 (42)	31
	50 and over ..	10 (83)	2 (17)	8 (67)	4 (33)	12
	Total	45	10	32	23	55

Table V shows that in both the treated and the control cases a little less than 20 per cent of patients had moderate or severe flushing before the menopause, except in the case of women between the ages of 45 and 49 who subsequently had the menopause induced when 33 per cent had moderate or severe flushing. (This difference, however, may be due to chance.)

After the menopause the incidence of moderate and severe flushings increased in both treated and control cases. The increase was greatest in age group 44 years or less where it rose from 17 to 50 per cent, and least in the age group 50 years or more, but again the differences may not be statistically significant.

Only 6 cases (5 treated and 1 control) were under 40 years of age at the time of the menopause and they have been included in the age group 44 years or less. Since, however, most gynaecologists think that severe symptoms usually follow induction of the menopause at this age, it was thought advisable to give details of these patients. Of the 5 treated cases, 2 had mild or no flushing, and 3 had moderate or severe flushing before the menopause.

After the menopause flushing was mild or absent in 1 and moderate or severe in 4 cases. The control case had moderate flushing before the menopause and mild after it.

From the figures it appears that the incidence of moderate or severe flushing decreases with the increase in age of the woman at the time of the menopause, and that there is no difference between the natural and the induced menopause in this respect.

(b) *Parity*. Three cases were excluded from each group because of incomplete information about parity or pre-menopausal flushing.

Since women with 2, 1 or 0 children were found to experience flushing of much the same severity both before and after the menopause they were grouped together and the findings compared with those in women with 3 or more children. As the numbers were relatively small, the cases with mild or no flushing and those with moderate or severe flushing were grouped together.

The findings are shown in Table VI. In both the treated cases and the controls, the incidence of more severe flushing before the menopause was twice as high in the women of higher parity as it was in those with small families or no children. After the menopause, the incidence of flushing rose in both parity groups, but to a much greater extent relatively in the women of lower parity, for they developed a higher incidence of severe flushing than did the women with large families.

It seems clear that, while women of low parity do not often have severe flushing before the menopause, about 50 per cent of them have afterwards so that in this group as a whole the disturbance caused by the menopause is greater than it is in women of higher parity, of whom many already have fairly severe flushing before the periods cease. There is no obvious explanation for these differences.

(c) *Pre-menopausal Flushing*. The severity of flushing before and after the menopause was compared and the findings are shown in Table VII. One of the control cases was excluded because the severity of flushing before the menopause had not been assessed.

Of the 77 treated cases and the 45 controls who had mild flushing before the menopause, 30 (39 per cent) and 15 (33 per cent) respectively developed more severe flushing afterwards.

By contrast, of the 24 treated cases and the 10 control cases who had moderate or severe flushing before radiation, 17 (71 per cent) and 8 (80 per cent) respectively continued to have more severe symptoms afterwards.

Nevertheless, some of the women who have bad pre-menopausal flushing improved once menstruation, either naturally or because of radiation, had ceased. Of the 34 women in the treated and control groups who had moderate or severe flushing before the menopause, 9 (26 per cent) experienced less severe flushing after it, even when the symptoms were at their worst.

(d) *Hormone Imbalance*. It was felt that patients with hormone imbalance, as suggested by the presence of cystic glandular hyperplasia of the endometrium, might experience flushing of different severity from those in whom the endometrium appeared to be normal. No signifi-

TABLE VI

Relationship between Parity and Severity of Pre-menopausal Flushing and of Post-menopausal Flushing at Its Worst

(Percentages in brackets)

	Total	Severity of Flushing	Before Menopause		After Menopause (At Worst)	
			Parity		Parity	
			0–2	3+	0–2	3+
Radiation Cases	98	Absent or Mild ..	37 (86)	39 (71)	21 (49)	31 (56)
		Moderate or Severe ..	6 (14)	16 (29)	22 (51)	24 (44)
		Total	43 (100)	55 (100)	43 (100)	55 (100)
Control Cases	53	Absent or Mild ..	18 (90)	26 (78)	11 (55)	19 (67)
		Moderate or Severe ..	2 (10)	7 (22)	9 (45)	14 (33)
		Total	20 (100)	33 (100)	20 (100)	33 (100)

TABLE VII

The Relationship between the Severity of Flushing Before and After the Menopause

(Percentages in brackets)

Severity before the Menopause			Severity after the Menopause (At Worst)	
			Mild or Absent	Moderate or Severe
Absent or Mild	Radiation Cases	77	47 (61)	30 (39)
	Control Cases	45	30 (67)	15 (33)
Moderate or Severe	Radiation Cases	24	7 (29)	17 (71)
	Control Cases	10	2 (20)	8 (80)

cant difference between the two groups was found.

From all these findings, it seems clear that the severity of flushing after the menopause is much the same whether this is induced or comes on naturally; and depends much more on the severity of the flushing before the menopause and on the age and parity of the patient.

Emotional State

Since the climacteric has a considerable emotional impact on most women, an attempt was made to find out how induction of the menopause affected the patients' emotional state and how this compared with what happened naturally.

Very simple methods were used. The emotional state before the menopause was first assessed. If the patient had always been calm and placid and gave no history of an emotional disturbance at any time, she was classed as "stable". If she had been irritable, depressed, easily upset or had a tendency to break into tears, she was classed as "unstable". Her emotional stability after the menopause was then assessed as being the same, better, or worse than before (*a*) at its lowest ebb, and (*b*) at the time of interview.

Three of the treated cases and 2 of the controls were excluded, because of doubt about the grading of the pre-menopausal emotional states.

The findings are shown in Table VIII. There was a higher incidence of emotional "instability" before the menopause in the women who required radiation, of whom 80·7 per cent were "unstable", than there was in the control cases, where the incidence was 63 per cent.

Of the 19 "stable" cases who had the menopause induced, only 2 became emotionally upset even at the worst, and by the time they were interviewed, both had recovered their mental poise. On the other hand, of the 20 "stable" cases who had a natural menopause, 10 were at some time emotionally disturbed and even at the interview 5 remained more easily upset than they had been before the periods stopped.

Of the 79 "unstable" cases who had radiation, even at the worst only 12 became more unstable, 53 noticed no change, and 14 felt better. By the time they were interviewed, only 4 were less stable than before, 37 were the same, and 38 were better. By contrast, of the 34 "unstable" controls, 14 were in even lower spirits after the menopause at the worst, 16 felt no difference, and only 4 were brighter. Even at the interview, 7 were still less stable than they had been before the menopause, 11 felt the same, and 16 were in better spirits.

It may be that where the climacteric is uncomplicated by functional haemorrhage the menopause is regarded with misgivings as heralding the end of reproductive life, but to the woman who is suffering from severe or prolonged menorrhagia, effective induction of the menopause is a welcome relief.

Sexual Feelings

As in the study of emotional factors, only simple methods of classification were used. The sex urge before and after the menopause was graded as strong, moderate, and slight or absent. An attempt was also made to find out whether

TABLE VIII

Emotional State Before and After the Menopause
(Percentages in brackets)

Emotional State	Before the Menopause		After the Menopause					
			At Worst			At Interview		
			Same	Better	Worse	Same	Better	Worse
Stable	Radiation Cases ..	19 (19·3)	17	—	2	19	—	—
	Control Cases ..	20 (37)	10	—	10	15	—	5
Unstable	Radiation Cases ..	79 (80·7)	53	14	12	37	38	4
	Control Cases ..	34 (63)	16	4	14	11	16	7

there had been any increase or decrease in desire either before or after the menopause. Twenty-two of the treated cases and 8 of the controls were either unmarried, widowed, divorced or separated from their husbands, and were therefore excluded. In 7 of the treated cases and 3 of the controls, the information obtained was thought to be unreliable. The findings in the remainder are shown in Tables IX and X.

Table IX shows that although approximately 70 per cent of the women had a moderate or strong urge before the menopause, only 30 per cent had the same desire after it. This reduction in the sex urge was not related to the type of menopause, for the findings in the cases who had radiation were almost identical with those in the controls.

Table X shows that, even before the menopause, 62 per cent of the women in both the treated and control groups had experienced some loss of desire. Of these, there was a further reduction in 51 per cent after radiation, and in 71 per cent after the natural menopause.

Of the patients who had retained their normal urge up to the menopause, 52 per cent noted a decrease after radiation. This incidence is precisely the same as that reported by McLaren (1950). In the equivalent control cases, however, there was some loss of desire in 47 per cent.

It has been shown that 60 per cent of all cases reported some loss of desire before the meno-

TABLE IX

Intensity of Sex Urge Before and After the Menopause
(Percentages in brackets)

	Total	Before the Menopause			After the Menopause		
		Absent to Slight	Moderate	Strong	Absent to Slight	Moderate	Strong
Radiation Cases ..	72	22 (30·6)	36 (50)	14 (19·4)	51 (70·8)	18 (25)	3 (4·2)
Control Cases ..	45	13 (28·9)	22 (48·9)	10 (22·2)	33 (73·3)	10 (22·2)	2 (4·5)

TABLE X

Alteration in Sex Urge Before and After the Menopause
(Percentages in brackets)

	Total	Before Menopause		After Menopause	
Radiation Cases	72	Reduced	45 (62)	Further Reduced ..	23 (51)
				Unaltered	21 (47)
				Increased	1 (2)
		Unaltered	27 (38)	Reduced	14 (52)
				Unaltered	13 (48)
		Increased	—		
Control Cases	45	Reduced	28 (62)	Further Reduced ..	20 (71·4)
				Unaltered	8 (28·6)
		Unaltered	17 (38)	Reduced	8 (47·1)
				Unaltered	6 (35·3)
				Increased	3 (17·6)
		Increased	—		

pause. Further changes appeared to bear little relation to the type of menopause, either artificial or natural. In approximately 50 per cent of cases in both groups, there was loss of desire after the menopause whether or not it had been affected previously. Three of 17 patients who had noted no falling off in the sex urge before the menopause reported an increase in desire after the natural menopause.

Dyspareunia

McLaren (1950) has published evidence suggesting that the incidence of dyspareunia after the radium menopause is greater than would occur naturally, because of undue closure of the fornices and vaginal stenosis. He reported an incidence of 10 per cent in his cases.

In this investigation, the cases studied were the same as those in Tables IX and X, except that another case was excluded from the treated group because information about dyspareunia was not obtained.

In Table XI it is seen that 15 (21 per cent) of the radiated patients and 6 (14 per cent) of the controls had pain during coitus after the menopause. Since 14 (20 per cent) of the radiated cases and 5 (11 per cent) of the controls had similar pain before the menopause, it is doubtful whether structural changes in the vagina resulting from the menopause, natural or induced, are of much importance.

Vaginal Discharge

Many believe that induction of the menopause by radium often causes a vaginal discharge. In this study, patients who suffered from a discharge before the menopause were asked whether it was cured, improved, unchanged or worse after the menopause; patients who had no pre-menopausal discharge were asked if they had remained free from discharge or had developed it.

Table XII shows that half the patients in both treated and control groups had vaginal discharge

TABLE XI

Incidence of Dyspareunia Before and After the Menopause

	Total	Dyspareunia	Before Menopause		After Menopause	
			No.	Per cent	No.	Per cent
Radiation Cases ..	71	Present	14	20	15	21
		Absent	57	80	56	79
Control Cases ..	45	Present	5	11	6	14
		Absent	40	89	39	86

TABLE XII

Incidence of Vaginal Discharge Before and After the Menopause
(Percentages in brackets)

Vaginal Discharge	Before Menopause		After the Menopause				
			Same	Improved	Cured	Worse	Only after Menopause
Present	Radiation Cases	56 (55·5)	2 (3·6)	18 (32·1)	35 (62·5)	1 (1·8)	—
	Control Cases	28 (50·0)	6 (21·4)	2 (7·1)	18 (64·3)	2 (7·1)	—
Absent	Radiation Cases	45 (44·5)	38 (84·4)				7 (15·6)
	Control Cases	28 (50·0)	27 (96·4)				1 (3·6)

before the menopause. Of these, over 60 per cent were completely cured after both the natural or induced menopause. After radiation, a further 32 per cent noted improvement, but this occurred in only 7 per cent of the control cases. Only 6 per cent of the treated cases reported the discharge as unaltered or worse after the menopause, as compared with 30 per cent of the controls.

A different trend is seen in the cases where there was no pre-menopausal leucorrhoea. Of the 45 women who had the menopause induced, 7 (15·6 per cent) developed discharge, compared with only 1 (3·6 per cent) of the 28 control cases. In 3 of the radiation cases there was a moderate vaginitis. One was due to *Trichomonas vaginalis* and was effectively treated by arsenical pessaries. In the other 2, the vaginitis was thought to be predisposed to by lack of oestrogens, and oestrogen therapy rapidly cleared up the discharge.

In 3 of the remaining 4 cases, the discharge was very slight and its presence was elicited only by specific questioning. Examination showed a very mild vaginitis in one case, but no abnormality of the vaginal mucosa or cervix was found in either of the others. None of these women desired treatment, for the discharge was apparently very slight and did not cause discomfort. In the fourth case a "moderately profuse discharge" was reported, but the patient refused to be examined and thought that treatment was unnecessary.

In the control case, a profuse, white, irritating discharge had developed and treatment with penicillin and sulphonamide pessaries had been instituted by her doctor. It had improved considerably, although a mild degree of vaginitis was seen on examination at the time of the investigation.

Erosion or chronic infection of the cervix is the most common cause of vaginal discharge in women. The figures just quoted show that it is a common condition just before the menopause and that it clears up in many cases after the periods cease. This investigation suggests that the discharge is more likely to be cured where the menopause is induced than when it occurs naturally. On the other hand, vaginal discharge is more likely to develop for the first time where the menopause is induced by radium, although this is not common nor is it serious.

Summary

An investigation has been carried out on 101 cases where the menopause has been induced by radiation, and on 56 cases where the menopause has occurred naturally, the interval between the cessation of menstruation and the time of interview being comparable in the two groups.

When the incidence of various symptoms in each group was compared and contrasted, it was found that:

(1) The incidence of post-menopausal flushing, particularly of the more severe grades, was almost the same in both groups, varying largely with the degree of the pre-menopausal disturbance.

(2) While there was a greater incidence of emotional instability before the menopause in the group treated by radiation, there was much less depression after the menopause in those patients than was found in control cases.

(3) Loss of sexual desire before the menopause occurred in over 60 per cent of all the cases investigated. A further loss occurred in 50 per cent of the remainder after the menopause whether this was natural or artificially induced.

(4) The incidence of dyspareunia after the menopause was closely related to the pre-menopausal incidence, and artificial induction of the menopause was not an aetiological factor.

(5) Vaginal discharge is more often cured in the cases treated by radiation than in those where the menopause is natural. On the other hand, women are less likely to develop vaginal discharge for the first time after a natural menopause than after radiation. It is, however, a very minor problem even in the irradiated group.

Conclusions

The findings in this investigation suggest that the use of radium to induce the menopause (X-rays were used in only 4 of the 101 cases) in women over 40 years of age produced almost the same subjective effects as does the natural menopause.

In deciding whether to treat profuse and irregular bleeding in women over 40 years of age

by radiation or hysterectomy, other factors besides those dealt with here have to be considered, such as the reliability of the method, the operative mortality, and the remote morbidity, especially the risk of cancer. These aspects have all been examined, and the findings will be published in a subsequent paper.

The results presented here, however, support the view that one should not be deterred from inducing the menopause by radium or X-rays by the fear that menopausal symptoms will be appreciably worse than those which the patient would experience if she passed through the menopause naturally.

Acknowledgments

I am most grateful to Professor Baird for the interest he has shown in this work and for his constant encouragement; to Professor W. M. Millar and Dr. M. Valentine of the Department of Mental Health for much practical guidance and demonstration; and to Mrs. Margaret Knight of the Department of Psychology for invaluable advice and criticism.

References

Barrett. *8th French Congress of Obstetrics and Gynaecology* as quoted by Phillips, L. (1938): *Proc. R. Soc. Med.*, **31**, 996.

Corscaden, J. A., Fertig, J. W., and Gusberg, S. B. (1946): *Amer. J. Obstet. Gynec.*, **51**, 1.

Hunter, W. (1939): *J. Obstet. Gynaec. Brit. Emp.*, **40**, 261.

McLaren, H. C. (1941): *J. Obstet. Gynaec. Brit. Emp.*, **48**, 1.

McLaren, H. C. (1950): *Brit. med. J.*, **2**, 76.

Malpas, P. (1937): *J. Obstet. Gynaec. Brit. Emp.*, **44**, 86.

Medical Women's Federation (1933): *Lancet*, **1**, 106.

Schmitze, H. E., and Towne, J. E. (1947): *Amer. J. Obstet. Gynec.*, **53**, 199.

Speert, H., and Peightal, T. C. (1949): *Amer. J. Obstet. Gynec.*, **57**, 261.

Werner, A. A.: *J. Missouri St. med. Ass.* as quoted by Donaldson, M. (1938): *Proc. R. Soc. Med.*, **31**, 1009.

THE TREATMENT OF 850 CASES OF SIMPLE UTERINE HAEMORRHAGE BY INTRA-UTERINE APPLICATION OF RADIUM

BY

WALLACE BARR, B.Sc., M.B., M.R.C.O.G.

Assistant Gynaecologist
Western Infirmary, Glasgow

AND

ALEXANDER A. CHARTERIS, M.B., D.P.H., F.R.F.P.S.G., F.F.R.

Director of Radiotherapy Department and National Radium Centre, Western Infirmary, Glasgow
Regional Consultant for South-West Scotland

THE induction of an artificial menopause by the use of radium is very frequently carried out in the treatment of excessive functional uterine bleeding especially when this occurs about the time of the menopause, but for many years there has been controversy as to whether this method of treatment is preferable to surgery or not. The results obtained are generally admitted to have been satisfactory as regards control of the haemorrhage but there are those who criticize the method on the grounds that it produces various unpleasant sequelae including unusually severe menopausal symptoms, local tissue necrosis and even an abnormal incidence of uterine neoplasms.

At the present time when many gynaecological departments have long waiting lists it seems to us that if these criticisms can be refuted the method has much to commend it, since it greatly reduces the use of hospital beds, as well as the period of incapacity suffered by the patient. It was, therefore, decided to submit the whole question to an impartial analysis by studying the results obtained at the Western Infirmary of Glasgow during the years 1926–1949 when 850 cases were treated by intra-uterine application of radium. This method of treatment has always seemed to us a desirable one and the diagnostic dilatation and curettage which is an essential preliminary to the treatment of uterine haemorrhage offers an opportunity to apply the radium at the same time. In the very rare event of the histological diagnosis differing from the clinical one, for example by indicating carcinoma of body of uterus, no harm is done since hysterectomy can be undertaken soon after, and indeed it is now a recognized procedure for some gynaecologists in this region to ask for such treatment as a preliminary to the operation so that the risk of escape of tumour cells at operation and of local recurrence may be diminished. No such unexpected case of carcinoma was found in this series although this quite exceptional occurrence has been encountered in recent years.

Our favourable impression of the use of radium does not imply criticism of treatment by X-rays, and this alternative method of inducing an artificial menopause is, in fact, used in this hospital with much the same degree of success, especially when out-patient attendance is preferable as in the case of patients who come from an adjacent town where the diagnosis has already been confirmed by the gynaecologist there. Our experience is that there is little to choose between the methods, but it is of interest to note that Hunter (1939) and others have the impression that intra-uterine application of radium may be accompanied by less upset in the general health of the patient as well as being more efficient in controlling the haemorrhage. Malpas (1937) also emphasizes as we have done that the diagnostic curettage can be combined with radium insertion, and he claims that this gives greater assurance of permanent amenorrhoea as well as being followed by less danger of development

of body carcinoma: this view is shared by Naujoks and Hoffmann (1934).

Technique

The method follows the lines adopted by many workers, and the radium applicator is of a well known type, being 6·6 cm. long with the usual slight curvature. It has an active length of 4·4 cm., filtration of 3 mm. silver and a radium content of 50 mg. (expressed as element). It is used with a rubber sheath at the surface of which the calculated dose rate is 406 r per hour. This falls off very quickly and the dosage at the position of the ovaries will probably not exceed 200 r over the total time of insertion (30 hours), although this will obviously depend upon the rather variable position of these organs. Some local effect from the treatment will very likely share in arresting the haemorrhage.

After routine cleansing of the parts a bimanual examination of the pelvic organs is carried out, the cervix then being dilated and the uterus curetted. The radium tube, sterilized by boiling and attached to a stout double silk thread, is inserted by a suitably designed instrument and retained by a single length of sterile gauze packing soaked in proflavine oleate (1 per cent in liquid paraffin), since we believe that this antiseptic is of value in preventing septic complications (Charteris, 1937). The packing not only keeps the tube in position but tends to displace the rectum from its immediate vicinity: no anchorage by stitching is found necessary. Excessive pressure from the packing is to be avoided since this not only causes discomfort but can produce damage to the mucous membrane by mechanically impairing the blood supply. A self-retaining catheter is next inserted and the silk threads secured by adhesive tape to the inside of the thigh after which a perineal pad and T-bandage are applied. During the time the radium is *in situ* the patient is nursed on her back and the knees secured together, while morphine sulphate ¼ gr. is usually given hypodermically on the evening of operation and the patient kept under close observation. The radium is left in the uterus for 30 hours and an aperient is given on the evening of withdrawal but no douche is permitted until the following day when one of acriflavine 1 in 1,000 (watery solution) is administered. The patient is kept in bed for 2 days after the conclusion of irradiation and is normally discharged on the sixth day after treatment.

Cases have been followed up routinely for 2 years and are only dismissed at the end of that time if free from symptoms, being then instructed to report back immediately if there is any further bleeding or any complaint of a gynaecological nature. The follow-up arrangements ensure that in the event of a patient not reporting on the appropriate date, she is sent for again and, if necessary, enquiries are also made through her own doctor. The follow-up is controlled by a chronological card index system and good clinical records are almost always ensured though it should be appreciated that this was not always so in the earlier years. The information obtained will now be discussed.

Age Groups

In Table I the 850 cases have been subdivided into age groups, and it will be seen that just over 15 per cent were under the age of 40 at the time of treatment. Nearly all these cases were dealt with early in the series when radiotherapeutic methods were at an early stage of development and records had not accumulated to give experience, but it soon became a well established rule that one does not undertake this treatment in women under the age of 40, and now as a result of the present investigation we believe that 42 is the lowest age at which the artificial menopause should be induced (vide infra).

Table I

Age Groups

		Per cent
Under 30	5	0·6
31–40	124	14·7
41–50	605	71·1
Over 50	116	13·6

Symptomatology

The symptoms complained of are summarized in Table II. All the patients presented bleeding of some type, and it will be seen that just over half the total number had irregular periods. A

TABLE II

Symptoms

		Per cent
Menorrhagia	314	37·0
3 months–6 months 111		
6 months–2 years 163		
More than 2 years 40		
Metrorrhagia	441	51·8
3 months–6 months 261		
6 months–2 years 99		
More than 2 years 81		
Continuous bleeding following regular normal periods		
2–4 weeks duration ..	51	6·0
5–8 weeks duration ..	44	5·2
Additional Symptoms		
Vaginal discharge ..	98	11·5
Pain		
Backache	168	19·7
Lower abdominal ..	124	14·6

N.B.—Only 43 (5·1 per cent) complained spontaneously of pain.

TABLE III

Result of Pelvic Examination

		Per cent
No abnormality detected ..	346	40·7
Uterus enlarged (S.P. 3–4 inches)	360	42·4
Palpable fibroids	86	10·1
Mucous polypi of cervix ..	55	6·5
Chronic cervicitis (with or without erosion) ..	176	20·7
Enlarged or cystic ovaries ..	129	15·2
Vaginal cyst	2	0·2
Bartholin's cyst	3	0·4
Prolapse of some degree ..	174	20·4

further 37 per cent had menorrhagia and in the third and smallest group there were those suffering from variable spells of continuous bleeding. Other symptoms included vaginal discharge and pain which was generally felt in the lower abdomen but also occurred as a low backache: it is of interest to note that, out of the total number, only 43 patients volunteered the complaint of pain, the remainder speaking of it only after specific questioning. During the years in question no special enquiry was made regarding the presence of menopausal symptoms before treatment but it appears from more recent experience that a proportion of patients do experience these manifestations before any irradiation.

PELVIC EXAMINATION

Table III shows the results of the routine bimanual examination. This was carried out under anaesthesia prior to dilatation, and it will be seen that 82 per cent of the series had either no detectable abnormality or only slight enlargement of an otherwise apparently normal uterus. Ten per cent had fibroids, the maximum uterine enlargement corresponding to the size of a 3-months pregnancy, since it is considered that any case where the uterus exceeds this size calls for operation: this is in agreement with the views expressed by other workers (Cheron, 1909; Malpas, 1937; Martindale, 1937). About one-fifth of all cases had some degree of prolapsus uteri though many did not complain of this so that it was only observed during the routine examination. A similar proportion had some degree of chronic cervicitis with or without erosion, and it is of interest to observe that very few of these cases when examined after treatment showed persistence of the condition. Crossen and Crossen (1947) suggest preliminary cauterization of such erosions, but we consider this unnecessary.

HISTOLOGICAL FINDINGS

The curettings were always sent for histological examination and the results are shown in Table IV. More than half of the cases (54·2 per cent) showed no abnormality whatever and were subdivided approximately equally into the four physiological groups detailed in the Table under this heading: of those with definitely recognizable pathological findings by far the greatest number (27·1 per cent) showed some degree of cystic glandular hyperplasia.

The 2 cases of tuberculous endometritis shown are of special interest for in both the radium had been inserted and the treatment given before the histological report was obtained and the true nature of the condition appreciated. Careful follow up of the patients showed that each made an uninterrupted recovery without further bleeding or any manifestation of the tuberculous condition; they gained weight and had no complaint, being well 8 and 10 years respectively

TABLE IV
Histology of Curettings

		Per cent
Normal endometrium:		
Early reparative	121	14·2
Late reparative	116	13·7
Early secretory	120	14·1
Late secretory	104	12·2
Cystic glandular hyperplasia ..	230	27·1
Mixed reparative and secretory changes	20	2·4
Atrophic endometrium ..	35	4·1
Chronic endometritis	19	2·2
Tuberculous endometritis ..	2	0·2
Marked oedema of stroma ..	16	1·9
Endometrial polypi	5	0·6
Others (no report available or no curettings obtained or spoiled material)	62	7·3

after treatment. It is not suggested that the use of radium is recommended for such conditions, but the facts indicate that the presence of unsuspected tuberculous endometritis is not a contra-indication to the induction of an artificial menopause by radium, so that these cases present no better argument for routinely awaiting the histological report than do those of uterine carcinoma.

RESULTS OF TREATMENT

Table V indicates what has been achieved as regards the control of bleeding and it will be seen that 774 (91·1 per cent) of the 850 patients responded satisfactorily: the case of the younger

TABLE V
Results of Treatment

		Per cent
No further bleeding	413	48·6
One menstrual period after treatment	278	32·7
Two menstrual periods after treatment	60	7·0
More than 2 menstrual periods after treatment	17	2·0
Continuous bleeding after treatment (up to 7-weeks duration)	6	0·7
No bleeding for 6 months to 5 years when the periods recommenced (all under 36 years)	10	1·2
Lost from follow-up	10	1·2
Required further treatment ..	56	6·6

women will be discussed separately. Malpas (1937) states that only 2·2 per cent of his series failed to respond to a radium dose of 2,000 mg.-hours, but it should be noted that this dose cannot be compared with ours in the absence of information as to the linear intensity of the applicator.

In the largest group of 413 cases there was no further bleeding after irradiation but the majority of the remainder had one or more periods before finally reaching the menopausal state, and patients are warned about this possibility since they might otherwise be dismayed at continuance of menstruation after undergoing a procedure designed to stop it. Attention is drawn to the small group of 10 patients in whom amenorrhoea occurred for some time after treatment only to be followed by re-establishment of menstruation. All these patients were under 36 years of age at the time of treatment and the possibility of failure is one of the various arguments against attempted induction of an artificial menopause in those not close to or at the climacteric age.

One of these younger women is of special interest since she became pregnant after treatment. Her radium menopause had been induced 3 years before on account of severe menorrhagia which failed to respond to other measures and this was only done because the patient, then aged 35, refused an operation. For 6 months after treatment this woman had no further bleeding nor any menopausal symptoms and she felt very well, but at the end of this time the periods recommenced in a normal cycle, continuing for 18 months after which she was found to be pregnant. Except for a slight elevation of blood pressure during the last 4 weeks, her pregnancy was uneventful and X-ray of the abdomen showed what appeared to be a normal foetus, but 2 days before the expected date of delivery all foetal movements ceased suddenly and 24 hours later she was delivered of a stillborn child. Examination of the foetus and of the placenta gave no clue as to the cause for this occurrence.

Reference to the literature reveals statements regarding a high incidence of abortion and stillbirths in such cases, as is indicated in reports by Giles (1949), Mayeur (1942), Kane (1935),

Kelly (1931), Bret and Deplus (1945), although other authors such as Kaplan (1937), Mazer and Spitz (1935) and Murphy (1929) quote lower rates for such complications. As Muller (1933) and many others, such as various contributors to a recent Conference held in London (Spear, 1947), point out there is also a danger of genetic effects which might prejudice future generations and though the evidence is largely experimental, this is probably due to the recessive character of the mutations and the potential danger is too serious to ignore so that we believe irradiation unjustifiable if it is not intended to produce a permanent menopause. The thoughtful article on this subject by Ellis (1948) is well worth perusal.

Further Treatment

The treatment described failed to control the bleeding in only 56 cases so that further attention was necessary as is shown in Table VI. Twenty-one of these (Group A) were given a second

Table VI

Further Treatment

A. Further radium once	17 (all successful)
Further radium twice	4 (3 successful—1 failure)
B. Additional treatment by X-rays	17 (14 successful—3 failures)
C. Hysterectomy	17 (with the 4 failures noted above in addition)

radium application and this was successful in 17, while the remaining 4 patients were subjected to a third exposure which proved adequate in all but 1. Such multiple doses are not given nowadays, any further irradiation called for being administered by the external use of X-rays so as to limit the dosage within the uterus which is, however, an organ very resistant even to considerable irradiation. Group B consists of 17 patients who had additional treatment in the form of X-ray therapy in dosage suitable for induction of the menopause and 14 responded to this. There were, therefore, 4 failures in Groups A and B and these were eventually treated by hysterectomy.

A further 17 cases had no further irradiation fater the initial treatment but were subjected to hysterectomy and, with the 4 failures noted above, this makes a total of 21 cases in the series where operation was required. The remaining patient of the 56 was a woman aged 46 years whose main complaint was of uterine bleeding. She had treatment with radium at the request of the consultant physician, although it was appreciated that her metrorrhagia was a manifestation of thrombocytopenic purpura and she died 3 months after the treatment which, as expected, did not reduce the haemorrhage.

Complications

Table VII shows the immediate post-operative complications which were encountered. Most patients were uncomfortable while the radium was *in situ* and complained of feeling nauseated

Table VII

Immediate Post-operative Complications

Cystitis	6
Proctitis	2
Thrombo-phlebitis of leg	2
Acute vaginitis	4
Severe pyrexia	1

and rather unwell, but removal of the packing and tube gave rapid relief from these symptoms. Such complaints, occurring in uncomplicated cases, are probably due to the mechanical effect of the applicator in the uterus and to the pressure of the vaginal packing since the volume of tissue treated is so small that constitutional upset from actual irradiation would hardly be possible. Six cases had acute cystitis following treatment and, of course, this may well have been due to the presence of the self-retaining catheter: all of these responded to treatment by alkalis and sulphonamides. There were 2 cases of proctitis, one of whom had intermittent recurrence of symptoms over 5 years, and 2 patients developed thrombo-phlebitis of the leg 8 and 11 days respectively after being in theatre. In each of the latter the condition settled down within a short period, the treatment being by rest, local heat and systemic penicillin. Four patients had acute vaginitis following treatment with a profuse purulent discharge but 3 cleared within 2 weeks while the fourth responded to

local treatment with gentian violet (1 per cent aqueous solution). The remaining patient showing untoward symptoms developed a sudden severe pyrexia which appeared on the evening after treatment. The fever rose to 105·4 degrees Fahrenheit, remained at that level for 2 days and then rapidly fell to normal, but apart from slight headache there were no other symptoms and there seemed to be no after effects. The 2 cases of proctitis present the only evidence in the series of tissue damage, and indeed one would not expect to see anything of this kind at the dose level involved.

Incidence of Malignant Disease

Four patients (Table VIII) are known to have developed some form of neoplasm at a later date, but in only 2 of these did this affect the uterus, the other sites being in rectum and on skin of face. One of the uterine lesions was a carcinoma of the cervix which developed 10 years after treatment, and we are unaware of any evidence that the onset of such a lesion may be the sequel to treatment of uterine haemorrhage. This leaves only 1 patient in the series who had adenocarcinoma of body of uterus and this seems a very low incidence in 850 cases. It is only right to say, however, that follow-up investigation over many years would be called for before it could be stated with confidence that the final incidence is different from that to be expected in an untreated group. Such a long term follow-up of patients has been undertaken by Corscadden, Fertig and Guisberg (1946) who found that malignant tumours of the uterus developed in 36 out of a series of 1,100 patients treated for simple uterine haemorrhage: this investigation went on over a period of 25 years, the incidence being about 3 per cent.

Table VIII

Incidence of Malignant Disease

1. Carcinoma body of uterus	1 case— 3 years after treatment
2. Carcinoma cervix uteri	1 case—10 years after treatment
3. Carcinoma rectum	1 case— 4 years after treatment
4. Rodent ulcer right lower eyelid ..	1 case— 6 years after treatment

This problem continues to receive our attention, but it does not seem justifiable in the present state of knowledge to regard this alleged hazard as a contra-indication to treatment. The suggestion has been made that the local action of radium within the uterus as opposed to the action of X-rays may mask the development of carcinoma in that site and cause symptoms to be slow in developing, but we have no evidence to support this.

Menopausal Symptoms

The final question to be discussed is to what extent these patients suffered from menopausal symptoms and whether these were severe enough to render the radiational menopause undesirable. In an endeavour to assess their severity one of us (W.B.) has studied the clinical records with an impartial mind to see what the follow-up examinations revealed, and we have also tried to get some idea of what the normal incidence of such symptoms may be. A valuable symposium on the artificial menopause (Gilmour *et al.*, 1949) gives much information on this subject, and from large numbers of cases the balance of opinion seemed to be that menopausal symptoms were not a serious problem, though in the discussion which followed McLaren (quoted below on the normal incidence of menopausal symptoms) stated that no less than 47 per cent of women so treated were seriously upset by menopausal symptoms. In a clinical investigation of this sort it is difficult to assess such symptoms accurately as regards severity or mildness, and we have attempted to make this distinction by classing them as severe if the patient made the complaints spontaneously and as mild if their existence had to be elicited by appropriate questioning. An element of instability and anxiety was frequently noted in patients who had the worst complaints.

Table IX gives details of the symptoms and it will be seen at once that 18·4 per cent of all the patients had severe symptoms. This does not seem a high incidence, but we have tried to compare it with what would be expected naturally. In a survey carried out by the Council of the Medical Women's Federation (1933) it is stated that only 15·8 per cent of 1,000 women

TABLE IX

Menopausal Symptoms

		Per cent
No complaint on questioning ..	482	56·7
Flushings as main symptom (mild) ..	92	10·8
Flushings as main symptom (severe)	71	8·3
Headaches as main symptom (mild)	21	2·5
Headaches as main symptom (severe)	41	4·8
Flushings + headaches as main symptom (mild)	51	6·0
Flushings + headaches as main symptom (severe)	45	5·3
Sweating as main symptom	2	0·2
Arthritis	11	1·3
Depression	9	1·1
Weight increase	4	0·5
Abdominal distension	6	0·7
Sleeplessness	4	0·5
Peripheral neuritis	1	0·1
Pruritus ani	1	0·1
"Tingling all over"	1	0·1
Burning feeling in vagina	4	0·5
Lost from follow-up	22	2·5

This Table is intended to indicate the dominant symptoms. It will be noted that the number lost from follow-up increased from 10 (Table V) to 22 as time has gone on.

investigated experienced the menopause without menopausal symptoms while 10 per cent had symptoms of such severity that they were incapacitated. This figure would appear to include the worst types and presumably cannot be compared with what we have based as severe, but it does give some idea of what may be expected. McLaren (1941), who is quoted above, gives 17 per cent for the incidence of severe symptoms after the natural menopause and Schultz and Towne (1947) give a figure of 21·2 per cent, so that allowing for personal differences in assessment, our figure of 18·4 per cent for the treated cases seems to compare quite favourably, especially when it is recalled that 15 per cent of our patients were under 40 years of age for reasons already explained. The age of the patient has an important relationship to the question of such symptoms since we found that there was a much higher incidence of severe symptoms in patients under 42 years of age and we should, therefore, expect a still lower incidence in our more recent cases. It is this finding which has led us to suggest that 42 is the lowest age at which the artificial menopause should be induced.

CONCLUSIONS

A short anaesthetic, a negligible period of indisposition, and a correspondingly brief occupancy of a valuable hospital bed, together with freedom from the discomfort of a major operation with its slight but definite risk, are all advantages which cannot be ignored. As a result of our investigations we have no hesitation in recommending the treatment of functional uterine haemorrhage with radium for any woman not less than 42 years of age in the absence of a very few contra-indications such as large fibroids or pelvic sepsis.

SUMMARY

During the years 1926–1949 850 patients were treated at the Western Infirmary of Glasgow by cavitary radium for simple uterine haemorrhage and this series is reviewed. The method is described and details given of symptoms, clinical findings and histology.

A satisfactory result from the primary treatment was achieved in 774 cases, while 56 required further treatment. Menstruation was re-established in 10 additional cases, each of whom belonged to a younger age group than would now be treated, and 22 patients were lost from the follow-up. There were no deaths and post-operative complications were few in number.

The incidence of malignant disease in the uterus after this form of treatment is discussed and it is concluded that no contra-indication to the method exists from this point of view. The incidence of menopausal symptoms is studied and no evidence is found for the belief that these are unusually severe or greatly different from what might be expected naturally.

NOTE

During the period under review the late Dr. Adam Barr was in charge of the Gynaecological Wards at the Western Infirmary of Glasgow. He thought highly of the method described and used it freely then and in subsequent years.

Addendum

Since this paper was completed 1 more patient has been found to develop carcinoma of body of uterus, and the incidence of this disease in treated cases is, therefore, 2 in 850 patients.

References

Bret, J., and Deplus, J. (1945): *Presse méd.*, **53**, 255.

Charteris, A. A. (1937): *Lancet*, **2**, 627.

Cheron (1909): *Obstétrique* (quoted by Malpas, 1937).

Corscadden, J. A., Fertig, J. W., and Guisberg, S. B. (1946): *Amer. J. Obstet. Gynec.*, **51**, 1.

Crossen, R. J., and Crossen, H. S. (1947): *J. Amer. med. Ass.*, **133**, 593.

Ellis, F. (1948): *Brit. J. Radiol.*, **21**, 1.

Giles, A. M. (1949): *J. Obstet. Gynaec. Brit. Emp.*, **56**, 1041.

Gilmour, M. D., Tod, M. C., Charles, A. H., Martindale, L., and McLaren, H. C. (1949): *Proc. R. Soc. Med.*, **42**, 311.

Hunter, W. D. (1939): *J. Obstet. Gynaec. Brit. Emp.*, **46**, 261.

Kane, H. F. (1935): *Amer. J. Obstet. Gynec.*, **29**, 264.

Kaplan, I. I. (1937): *Amer. J. Obstet. Gynec.*, **34**, 420.

Kelly, H. A. (1931): *J. Amer. med. Ass.*, **97**, 760.

McLaren, H. C. (1941): *J. Obstet. Gynaec. Brit. Emp.*, **48**, 1.

Malpas, P. (1937): *J. Obstet. Gynaec. Brit. Emp.*, **44**, 86.

Martindale, L. (1937): *J. Obstet. Gynaec. Brit. Emp.*, **44**, 109.

Mayeur, M. H. (1942): *J. Obstet. Gynaec. Brit. Emp.*, **49**, 542.

Mazer, C., and Spitz, L. (1935): *Amer. J. Obstet. Gynec.*, **30**, 214.

Medical Women's Federation (1933): *Lancet*, **1**, 106.

Muller, H. J. (1933) *in* Glasser, O. (ed.): *The science of radiology*. Baillière, Tindall & Cox, London. p. 305.

Murphy, D. P. (1929): *Amer. J. Obstet. Gynec.*, **18**, 179.

Naujoks, H., and Hoffmann, H. (1934): *Zbl. Gynäk.*, **58**, 1222.

Schultz, H., and Towns, I. (1947): *Amer. J. Obstet. Gynec.*, **53**, 205.

Spear, F. G. (ed.) (1947): *Certain aspects of the action of radiation on living cells. Brit. J. Radiol. Suppl.*, 1.

PHAEOCHROMOCYTOMA AND THE OBSTETRICIAN

BY

SIR ARTHUR A. GEMMELL, *M.C.*, *T.D.*, P.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Liverpool

A PHAEOCHROMOCYTOMA is a localized growth of the adrenal medulla which is functionally active in that it produces adrenaline and noradrenaline. Such tumours are sometimes bilateral and occasionally malignant.

My active interest in the condition was stimulated by a case on my service at the Liverpool Maternity Hospital. The following is an account of her case history:

*Mrs. V.C.** Aged 24. She came under observation in August, 1951, in her fifth pregnancy.

First pregnancy, 1947: Slight attack of pyelitis at 16 weeks, otherwise normal. Normal delivery. Living child 6 pounds 7 ounces.

Second pregnancy, 1948: Some nocturnal breathlessness during pregnancy. Normal delivery. Living child 7 pounds 8 ounces. On sixth day severe headache, blood pressure not recorded; similar episode 36 hours later.

Patient stated during investigation in 1951 that attacks have occurred from time to time characterized by intense headache, sweating, feeling of weakness, breathlessness and sense of apprehension.

Third pregnancy: Spontaneous abortion at 12 weeks.

Fourth pregnancy, 1950: Complained of breathlessness during pregnancy. Normal delivery. Living child 7 pounds 15 ounces. Postpartum haemorrhage about 40 ounces. On third day severe headache and backache, shaking all over, pale and vomited. Blood pressure not recorded.

Fifth pregnancy, 1951: Seen in antenatal clinic at 34th week on account of twin pregnancy. Confirmed by X-ray. Blood pressure 146/80 mm. Hg. Admitted 6th September in labour. Urine albumen-free. Blood pressure 142/78 mm. Hg. Spontaneous twin delivery. Live children 7 pounds 2 ounces and 5 pounds 13 ounces. Severe headache following birth of first twin. Six hours later blood pressure 200/110 mm. Hg. Ten hours after delivery headache still severe, blood pressure 190/110 mm. Hg, vomiting, albumen present in urine. Fourteen hours after delivery blood pressure 110/70 mm. Hg.

On seventh day post-partum had a "fit". Blood pressure rose to 235/120 mm. Hg.

Thereafter attacks of severe headache with sweating and very labile blood pressure.

A typical attack is described as follows:

Palpitations are first felt with severe headache, her head throbbing and she is conscious of a swishing noise synchronous with the pulse. She becomes breathless and feels afraid. Aching develops in the epigastrium with nausea and frequently vomiting. The face feels hot and flushed, the hands go white, sweating occurs and she has some photophobia leading into convulsive movements and unconsciousness. The acute phase is followed by dull headache and lumbar backache for some hours.

Investigations showed that 0·025 mg. of histamine would induce an attack. The fall of blood pressure on injection of Piperoxane was not dramatic. Perirenal pneumography demonstrated a large rounded tumour in the region of the right suprarenal. The tumour was removed by Professor C. A. Wells. A year later she was free from headaches and better than she had been for a long time. The blood pressure was 120/70 mm. Hg.

In 1954 she had another pregnancy but was not under our care. Our first knowledge of this pregnancy was a call for our "obstetric flying squad" to attend her on account of a post-

* Some features of this patient have already been recorded by Cadman and Tinckler (1953).

partum haemorrhage on 21st July, 1954. Fortunately this was small in amount and fairly easily controlled. It was then learnt that she had had a normal pregnancy and labour. She had some "heaviness" of her head during pregnancy. Blood pressure readings had been recorded: March 120/80, April 110/70 and May 110/70 mm. Hg; on the seventh day of the puerperium it was 125/80 mm. Hg.

Since seeing this patient two others have come within my knowledge. Through the courtesy of Dr. Baker Bates and Professor T. N. A. Jeffcoate I record Mrs. M.T., aged 32. She had had 2 children 8¼ years and 7 years ago respectively. An intensive enquiry has failed to provide any details of her condition during these pregnancies. She was seen in February, 1953, and complained that for the past year she had dyspnoea on exertion and a tight feeling in her throat. She cannot remember anything during the attacks of dyspnoea. She had also had bad headache. At first the attacks occurred once every 6 weeks, more recently every 2 to 3 weeks, but an attack was always brought on by excitement.

A nurse reported that during an attack her breathing was rapid, her pulse fast and she was pale and sweated. She then fell back unconscious for a few minutes but the attack might last for up to 2 hours.

On admission her blood pressure was 205/120 mm. Hg. On account of the nature and periodicity of the attacks a phaeochromocytoma was suspected. There was a slight fall in blood pressure when 1/40 mg. histamine was injected intravenously. A Piperoxane test was negative when the blood pressure was 160/110 mm. Hg. Repeated doses of sodium amytal were given when the blood pressure was 170/110 mm. Hg with the following result:

8.00 p.m.	B.P.	170/110. Sodium amytal gr. iii.
8.30 p.m.	„	170/110.
9.00 p.m.	„	170/110. Sodium amytal gr.iii.
9.30 p.m.	„	174/120.
10.00 p.m.	„	146/98. Sodium amytal gr. iii.
10.30 p.m.	„	158/100.

An intravenous pyelogram showed both kidneys to be normal.

An electro-encephalogram showed that at rest there was an occasional attempt at formation of an irregular low amplitude 11 per second alpha rhythm. In addition to this, there was a considerable amount of low amplitude slow activity largely within the theta range. The slow activity was more obvious during the third minute of hyperventilation. The slow activity is outside the limits of normal here, but this is a non-specific abnormality.

The foregoing tests did not confirm the presence of a phaeochromocytoma and as she was also complaining of menorrhagia and a small bladder calculus had been seen on X-ray examination it was decided to remove the stone by crushing and perform a curettage. These procedures were undertaken on 8th April, 1954. The anaesthetic used was Thiopentone, Nitrous oxide, oxygen, minimal Trilene and Scoline, and the patient died during the operation despite all attempts at resuscitation.

The significant lesions found at post-mortem examination were a phaeochromocytoma of the right adrenal gland, left ventricular hypertrophy and pulmonary collapse with oedema.

The phaeochromocytoma was confirmed histologically.

The other patient was Mrs. L.M., aged 32 years. She was seen on 23rd June, 1954, at the 37th week of her sixth pregnancy.

First pregnancy, 1944: Normal delivery. Living child 5 pounds 12 ounces.

Second pregnancy, 1947: Normal delivery. Living child 7 pounds 8 ounces.

Third pregnancy, 1950: Normal delivery. Living child 6 pounds 15 ounces. Post-partum haemorrhage. Manual removal of placenta and blood transfusion.

Fourth pregnancy, 1952. During this pregnancy had attacks of faintness, persistent headaches accompanied at times by vomiting. Blood pressure taken in antenatal clinic varied between 110/70 and 130/80 mm. Hg. Normal delivery. Living child 8 pounds 13 ounces. Manual removal of placenta and blood transfusion.

Fifth pregnancy, 1953: Spontaneous premature labour at 7 months. Stillborn child before the doctor's arrival.

Careful enquiry has not elicited any information about the presence or absence of toxaemia during her pregnancies.

Mrs. L.M. was seen for the first time in the

antenatal clinic on 23rd June, 1954. She had a normal pregnancy of 37 weeks' duration. Her blood pressure was 135/85 mm. Hg but albumen and acetone were present in the urine. Admission was arranged for the following day.

On admission on 24th June her blood pressure was 170/100 mm. Hg and there was "a cloud" of albumen. She then admitted to attacks of vomiting every few days associated with headaches. There was no oedema.

On the 25th her blood pressure varied between 160/95 and 170/105 mm. Hg. Her blood urea was 36·4 mg. per 100 ml.

The blood pressure reading on the morning of 26th June was 160/110 mm. Hg. At 11.0 p.m. that evening she complained of pain in the right side and headache. Her blood pressure had risen suddenly to 220/120 mm. Hg. The right side of the abdomen was extremely tender. On a diagnosis of fulminating toxaemia with accidental haemorrhage an immediate Caesarean section was undertaken. The anaesthetic was Kemithal, Flaxedil, Nitrous oxide and Oxygen. A little Cyclopropane was used. Delivery of a living child of 4 pounds 13 ounces was followed by the difficult removal of a pathologically adherent placenta. There was no evidence of accidental haemorrhage. At this stage the blood pressure was 220/160 mm. Hg, the pulse rate 160 per minute, and the patient was showing some cyanosis. From this point the general condition deteriorated and all attempts at resuscitation failed. The patient died.

The significant lesions at post-mortem examination were left ventricular hypertrophy, pulmonary collapse with oedema and a phaeochromocytoma of the right adrenal. There had been a haemorrhage into the tumour which explained the right-sided pain. The phaeochromocytoma was confirmed histologically.

The kidneys were histologically examined in great detail but no changes were found resembling those occurring in toxaemia.

John B. Graham (1951) published a review of phaeochromocytoma but did not particularly examine the facts in regard to childbearing in the female patients. In earlier writings it had been suggested that the condition occurred predominantly in females but Graham collected details of 112 women and 94 men.

For this study I have been able to examine particulars of 212 female patients. This material has been obtained from the literature (predominantly American) often supplemented by correspondence and from case histories kindly supplied to me personally but not yet published, including 9 from the Department of Pathology in the University of Melbourne. From this number 8 are totally excluded either because there was some doubt about the condition or because the organ of Zuckerkandl was the affected structure and not the adrenal medulla.

Unfortunately all the details are not available for each patient, consequently the totals vary in the subsequent paragraphs.

Age Incidence

Twenty-two patients were aged up to and including 19 years. The distribution within this age group is interesting. There is 1 child aged 5 months, a group of 13 in the ages 10-14 years both inclusive and the remaining 8 are aged 17-19 years both inclusive.

These data suggest that there is an underlying genetic factor in the condition and that it tends to be wakened into activity at times of endocrine development. Obviously 10-14 is the time of puberty and the range 17-19 that at which it is often asserted, though not proved, that menstruation changes from the anovular to the ovular type.

From the age of 20 upwards there are 174 patients but of these symptoms only developed after the age of 50 in 27. Consequently we must accept that if the cause is genetic the tendency may remain latent for very many years.

Familial Tendency

There is a slight suggestion that there may be a familial tendency to the condition. Calkins and Howard (1947) have reported 2 patients, one the maternal aunt of the other. Hunt and McConahey (1953) reported a patient who was one of three siblings all found to have bilateral phaeochromocytomas causing hypertension.

Age and Parity

In patients aged 20 upwards where both age and parity are known we get the distribution shown in the following table.

Age	Nulliparous		Parous	
	Number	Per cent of total nulli-parous	Number	Per cent of total parous
20–29 ..	28	52·8	19	25·0
30–39 ..	13	24·5	25	32·9
40–49 ..	6	11·3	12	15·7
50 upwards	6	11·3	20	26·3

In compiling this table patients have been assigned to the age and parity group of the time at which symptoms first appeared. Patients who had had abortions only are classed as nulliparous in order to correspond with Census figures.

As the majority of the cases are reported from the United States of America and are in white women, this age-parity distribution has been compared with that shown in the U.S.A. 1940 census figures for the total female white population and it does not differ significantly.

Preceding Toxaemia and Phaeochromocytoma

Amongst the total of 85 patients known to be parous there were 17 who had a toxaemia of pregnancy before the symptoms referable to the phaeochromocytoma developed (20 per cent). Amongst these 85 case histories there are 17 in which it has not been possible to obtain details of the condition of the patient during pregnancy. If these are deducted the incidence of a preceding toxaemia was 17 in 68 or 25 per cent. Whichever figure is taken it is considerably higher than that of 13 per cent which has recently been found to be the overall risk of a woman developing toxaemia at some time in her child-bearing career in the City of Liverpool (Gemmell, Logan and Benjamin, 1954).

In this context the varied incidence of toxaemia in different parts of the world must be stressed and it must be emphasized that the majority of the recorded cases are from the U.S.A. Further, it is doubtful if 20 to 25 per cent of 85 patients is statistically of significant difference from 13 per cent of 15,780 on which the Liverpool figures of 13 per cent are based.

Symptoms in Relation to Pregnancy

It is of importance to obstetricians that of 115 patients reported upon between the ages of 20 and 50 there was a close time relationship between a pregnancy and the final diagnosis in 35 patients (30 per cent).

The pregnancy order in which the patient was treated or died is shown below:

	Pregnancy							Total
	1	2	3	4	5	6	Order unknown	
Number of patients	12	11	5	1	1	3	2	35

This does not give the full picture because when the patients' histories are fully examined it becomes apparent that symptoms due to the tumour had been present in a number of cases before the pregnancy in which the diagnosis was made. The following table shows this:

Symptoms appeared	No.	Operation or death	Symptoms continued	Operation or Death					
				1st	2nd	3rd	4th	5th	6th
Before pregnancy	10	2	8	5	4	1			
1st pregnancy	9	7	2			2			
Between 1st and 2nd pregnancy ..	1				1				
2nd pregnancy	7	6	1					1	
3rd pregnancy	2	2							
4th pregnancy	1	1							
5th pregnancy	2		2						2
6th pregnancy	1								1
? pregnancy order	2	2							

It should be noted that the 2 patients who were operated upon before pregnancy had a normal first pregnancy but a second tumour appeared during their second pregnancies. This fact may also show a tendency for the genetic factor to remain latent for some time.

Irrespective of the date of onset of the earliest symptoms the relationship between pregnancy and the symptoms leading to diagnosis was as follows:

During pregnancy at varying periods between the third month and term			17
Immediately following delivery ..	6		
1st day post-partum	3		
5th day post-partum	1	14	
7th day post-partum	4		
19th day post-partum	1		
Unspecified day	3		

It will be noted that there are approximately as many patients who developed severe symptoms between labour and the 7th post-partum day as there were during pregnancy. In the 9 cases which were fulminating in the first twenty-four hours after delivery 8 died.

The symptoms recorded are shown below and compared in frequency with 100 cases recorded by Graham.

Symptoms	35 patients related to pregnancy	Percentage	Graham's 100 cases Per cent
Severe headache ..	28	80	55
Vomiting or nausea	14	40	36
Sweating	14	40	23
Palpitation ..	11	31·4	38
Blanching, particularly of limbs ..	7	20	16
Apprehension ..	6	17·1	3
Substernal or epigastric pain ..	6	17·1	12
Dyspnoea ..	5	14·3	19
Vertigo	3	8·6	15
Eye changes ..	3	8·6	8

Some other symptoms which only occurred once each.

It will be noted that the symptoms do not differ very much in the group of pregnant women compared with an unselected group of 100 patients of both sexes except possibly that the incidence of severe headache is higher. Accompanying these symptoms there is hypertension typically labile but sustained in some patients. The majority of patients have one or more hypertensive crises. There is unfortunately no common symptom pattern but the picture is frequently one of headache, vomiting or nausea, a raised blood pressure and hypertensive attacks which are taken to be fits, so it is not surprising that the differential diagnosis from eclampsia has been a difficulty. Although albumen was found in the urine of one patient this is not common and its absence should help to distinguish the two conditions.

It is tempting to think that there is some underlying cause common to this condition and to the toxaemias. Such an idea gets mild support from a paragraph in Hoogeveen's (1948) report of his fatal case. The patient died about a week before term. At the post-mortem examination changes were found in the liver that are described as showing "a striking resemblance to the liver degeneration found in fatal cases of eclampsia". There are, however, too many differences to warrant us following this suggestion further for, as has been said albuminuria is uncommon, oedema is very rare and no author has reported changes in the kidneys in fatal cases similar to those seen in fatal eclampsia.

If the tumour is not diagnosed and removed at the time of pregnancy and is not fatal, some of the patients experience a remission of their symptoms or a striking reduction in their severity. When the next pregnancy occurs, however, symptoms are again aggravated.

There must therefore be a different degree of activity of these tumours either in themselves or in their response to other changes in the body. The former view is supported by the varying amounts of adrenaline and nor-adrenaline found in tumours which have been removed, but this is not absolute for the method of assay is not always clearly stated. This view might also explain the cases in which symptoms appear only in a later stage of life. The appearance of symptoms at the time of puberty or of the supposed onset of ovulation in some patients is, perhaps, an indication of the latter view as is the appearance or recrudescence of symptoms as early as the third month of pregnancy in some cases whereas these are delayed until term or after in others.

There is yet another factor to be considered. If a patient has a tumour large enough to be palpable, massage of the tumour precipitates a hypertensive attack. Similarly handling of the tumour at an operation for its removal induces hypertension to such an extent that surgical writers advise that as soon as the tumour is exposed its blood vessels should be sought and tied, before the tumour itself is touched. Thus mechanical stimulation appears to flood the circulation with the tumour's secretion. It may therefore be that during labour the contractions of the uterus and the use of the secondary powers act mechanically upon the tumour and account for the group of cases in which the symptoms are so severe during labour and the succeeding twenty-four hours.

Diagnosis

As has already been shown, there is no clear symptom complex on which to make a diagnosis.

The present aids to diagnosis are:

(1) The production of a hypertensive attack by the intramuscular injection of histamine.

(2) The production of an immediate fall of at least 40 mm. Hg in the systolic blood pressure by an injection of Piperoxane, Dibenamine or Regitine. Alfred J. Barnett (1951) has pointed out the limitations and possible toxic effects of Dibenamine as a diagnostic agent. In patients with a labile blood pressure this test must be carried out when the pressure is at a peak rise.

(3) Outlining the tumour by perirenal pneumography.

Unfortunately, none of these tests is absolutely certain. Both false positive and false negative results occur.

The only certain method of diagnosis is the induction of a hypertensive attack by massage over the tumour in those patients in whom it is palpable—and such cases are small in number.

Treatment

Surgical removal of the growth is the treatment. The safeguards to be adopted during operation and in the post-operative period are fully described in the surgical papers and will not be repeated here.

Further Pregnancies after Removal of the Growth

Two patients who were single at the time of the operation each had a normal pregnancy 12 months and 18 months later respectively.

But this is not always the sequence. Two other patients were nulliparous at the time of operation, each then had 2 pregnancies. Each was quite fit in the first but the attacks were so severe in the second that labour had to be induced and a second operation performed. One of them then had another normal pregnancy.

Three parous women had the following post-operative histories:

(*a*) A normal pregnancy later.

(*b*) Two normal pregnancies later.

(*c*) The patient had been ill in her 2 pregnancies and bilateral tumours were then removed. After this she was put on treatment for cortical deficiency and had a normal pregnancy.

Comments

One of the gaps in our knowledge is that of the role of the adrenal medulla in pregnancy.

Even if we make the assumption that there is a genetic factor in the aetiology of phaeochromocytoma the facts here presented do not prove that pregnancy stimulates the full development of the condition. There are, however, pointers to the idea that the condition is apt to declare itself at eras of altered endocrine activity.

The symptoms associated with phaeochromocytoma are often difficult to distinguish from those of eclampsia. We must, however, be aware of this tumour as a cause of such symptoms because its removal will cure the patient.

Essential hypertension is, nowadays, often classed with the toxaemias and may indeed be a sequel to prolonged toxaemia.

A pregnant patient who shows hypertension as a dominant physical sign may therefore be suffering from toxaemia, essential hypertension or a phaeochromocytoma, so the last-named must be considered in the differential diagnosis.

It is worth remembering that the de Courcys (1952) have stated that in so-called malignant hypertension the proportion in which phaeochromocytomas occur is about 5 per cent or even higher.

We should therefore strive to improve the methods of diagnosis of this tumour and apply them in patients in whom the diagnosis is doubtful. Progress might be made by further research to determine the occurrence and nature of the pressor substances present in patients suffering from toxaemia.

ACKNOWLEDGMENTS

I desire to express my gratitude to the many colleagues who have sent me additional details of their reported cases and to those who have sent me records of cases so far not reported. Attention is drawn to their names in the Bibliography.

Much generous help was given by Mr. P. Wade, Librarian of the Royal Society of Medicine, and Mr. W. A. Lee, Librarian of the Liverpool Medical Institution, in the collection of articles in the literature for which I am also very grateful.

REFERENCES

Barnett, A. J. (1951): *Med. J. Aust.*, **1**, 939.
Cadman, E. F. B., and Tinckler, L. F. (1953): *J. Fac. Radiol.*, **4**, 211.
Calkins, E., and Howard, J. E. (1947): *J. clin. Endocrin.*, **7**, 475.
De Courcy, J. L., and De Courcy, C. B. (1952): *Staff. Conf. De Courcy Clin.*, **20**, 3.
Gemmell, A. A., Logan, W. P. D., and Benjamin, B. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 458.
Graham, J. B. (1951): *Int. Abstr. Surg.*, **92**, 105.
Hoogeveen, A. J. A. (1948): *Nederl. Tijdschr. Geneesk.*, **92**, 1681.
Hunt, A. B., and McConahey, W. M. (1953): *Amer. J. Obstet. Gynec.*, **66**, 970.

OTHER REFERENCES USED FOR THE COMPILATION OF FIGURES BUT NOT QUOTED IN THE TEXT

Band, D.: Personal communication.
*Barnett, A. J., Blacket, R. B., Depoorter, A. E., Sanderson, P. H., and Wilson, G. M. (1950): *Clin. Sci.*, **9**, 151.
Bartels, E. C., and Arnold, W. T. (1949): *Lahey Clin. Bull.*, **6**, 132.
Bartels, E. C., and Cattell, R. B. (1950): *Ann. Surg.*, **131**, 903.
*Bartels, E. C., and Kingsley, J. W. (1947): *Surg. Clin. N. Amer.*, **27**, 605.
Bartels, E. C., and Kingsley, J. W. (1948): *Lahey Clin. Bull.*, **6**, 7.
*Bauer, J., and Belt, E. (1947): *J. clin. Endocrin.*, **7**, 30.
Becker, M. C., Bass, R. D., and Robbins, C. M. (1949): *J. med. Soc. New Jersey*, **46**, 339.
*Belt, A. E., and Powell, T. O. (1934): *Surg. Gynec. Obstet.*, **59**, 9.
*Berkheiser, S. W., and Rappoport, A. E. (1951): *Amer. J. clin. Path.*, **21**, 657.
*Binger, W. M., and Craig, W. McK. (1938): *Proc. Mayo Clin.*, **13**, 17.
Biskind, G. R., Meyer, M. A., and Beadner, S. A. (1941): *J. clin. Endocrin.*, **1**, 113.
Bjuggren, S. (1947): *Nord. Med.*, **33**, 566.
*Blacklock, J. W. S., Ferguson, J. W., Mack, W. S., Shafer, J., and Symington, T. (1947): *Brit. J. Surg.*, **35**, 179.
Borch-Johnsen, E. (1937): *Acta chir. scand.*, **80**, 171.
Bowen, G. L., Grandin, D. J., Julien, E. E., and Krech, S. (1950): *Amer. J. Obstet. Gynec.*, **59**, 378.
Brenner, F., Konzetti, H., and Nagl, F. (1938): *Münch. med. Wschr.*, **85**, 914.
*Brines, O. A., and Jennings, E. R. (1948): *Amer. J. Path.*, **24**, 1167.
Bruce, G. M. (1948): *Arch. Ophthal.*, **39**, 707.
Brunschwig, A. (1938): *Surgery*, **4**, 361.
Brunschwig, A. (1940): *J. Amer. med. Ass.*, **115**, 355.
Brunschwig, A. (1947): *J. Amer. med. Ass.*, **134**, 253.
Burgess, A. M., Waterman, G. W., and Cutts, F. B. (1936): *Arch. intern. Med.*, **58**, 433.
*Cahill, G. F. (1944): *Surgery*, **16**, 233.
Cahill, G. F. (1948): *J. Amer. med. Ass.*, **138**, 180.
*Cahill, G. F. (1950): *J. Urol.*, **64**, 1.
*Cole, L. (1950): *Brit. Heart J.*, **12**, 232.
Colston, J. A. C. (1948): *J. Urol.*, **59**, 1036.
Console, A. D., Dunbar, H. S., and Ray, B. S. (1950): *Surgery*, **28**, 428.
Crowther, E. V. (1951): *Brit. med. J.*, **1**, 445.
*Davies, J. V. S. A. (1952): *Brit. med. J.*, **2**, 77.
*Decker, H. C., McDowell, F. W., and Trimble, I. R. (1951): *J. Amer. med. Ass.*, **147**, 642.
*Engel, A., and von Euler, U. S. (1950): *Lancet*, **2**, 387.
*Engel, F. L., Mencher, W. H., and Engel, G. L. (1942): *Amer. J. med. Sci.*, **204**, 649.
Ernould, H., and Picard, E. (1934): *Rev. belg. Sci. méd.*, **6**, 223.
Evans, V. L. (1937): *J. Lab. clin. Med.*, **22**, 1117.
Evans, W. F., and Stewart, H. G. (1942): *Amer. Heart J.*, **24**, 835.
*Fahmy, A. (1952): *Brit. med. J.*, **2**, 159.
Fingerland, A. (1942): *Virchows Arch.*, **309**, 218.
Flew, J. D. S.: Personal communication.
Fränkel, F. (1886): *Virchows Arch.*, **103**, 244.
Ganem, E. J., and Cahill, G. F. (1948): *New Engl. J. Med.*, **238**, 692.
*Geissindorfer, R. (1951): *Arch. klin. Chir.*, **267**, 167.
Gerwig, W. H., and Seeley, S. F. (1953): *Sth. med. J.*, **46**, 355.
Gifford, R. W., Roth, G. M., and Kvale, W. F. (1952): *J. Amer. med. Ass.*, **149**, 1628.
*Goldenberg, M., Snyder, C. H., and Aranow, J. (1947): *J. Amer. med. Ass.*, **135**, 961.
*Goldner, M. G. (1947): *J. clin. Endocrin.*, **7**, 716.
*Green, D. M. (1946): *J. Amer. med. Ass.*, **131**, 1260.
*Grimson, K. S. (1951): *Ann. Surg.*, **134**, 451.
Guarneri, V., and Evans, J. A. (1948): *Amer. J. Med.*, **4**, 806.
Gutmann, D. (1947): *Brit. med. J.*, **1**, 563.

* Supplemented by personal communication.

Halbfas-Ney, P. (1929): *Frankf. Z. Path.*, **37**, 468.
Hamilton, J. E. (1940): *Kentucky med. J.*, **38**, 572.
*Hamilton, M., Litchfield, J. W., Peart, W. S., and Sowry, G. S. C. (1953): *Brit. Heart. J.*, **15**, 241.
Hatch, F. N., Richards, V., and Spiegl, R. J. (1949): *Amer. J. Med.*, **6**, 633.
*Heath, F. K., Cahill, G., and Atchley, D. W. (1941): *J. Amer. med. Ass.*, **117**, 1258.
*Hegglin, R., and Nabholz, H. (1938): *Z. klin. Med.*, **134**, 161.
Hedinger, E. (1911): *Frankf. Z. Path.*, **7**, 112.
Herde, M. (1912): *Arch. klin. Chir.*, **97**, 937.
*Hick, F. K. (1933): *Arch. Path.*, **15**, 665.
Hoch, G. F. (1949): *J. Urol.*, **61**, 473.
Hoerner, M., and Fournier, [R.] (1937): *Bull. Soc. Obstét., Paris*, **26**, 687.
Holst, E. J. (1938): *Acta med. scand.*, **94**, 510.
*Hyman, A., and Mencher, W. A. (1943): *J. Urol.*, **49**, 755.
*Jelliffe, R. S. (1952): *Brit. med. J.*, **2**, 76.
Kahlan, G. (1936): *Frankf. Z. Path.*, **50**, 86.
*Kalk, H. (1934): *Klin. Wschr.*, **13**, 613.
Kaulbach, G. (1937): *Zbl. allg. Path. path. Anat.*, **67**, 49.
Kawashima, K. (1911): *Virchows Arch.*, **203**, 66.
Kelly, H. M., Piper, M. C., Wilder, R. M., and Walters, W. (1936): *Proc. Mayo Clin.*, **11**, 65.
Koster, E. F. (1945): *Ohio St. med. J.*, **41**, 729.
Kremer, D. N. (1936): *Arch. intern. Med.*, **57**, 999.
*Kvale, W. F., Roth, G. M., Clagett, O. T. and Dockerty, M.B. (1944): *Surg. Clin. N. Amer.*, **24**, 922.
Labbe, M., Violle, P. L., and Azerad, —. (1922): *Bull. Soc. méd. Hôp. Paris*, **46**, 982.
*Lazarus, J. A., and Eisenberg, A. A. (1932): *J. Urol.*, **27**, 1.
*Lian, C., Welti, H., and Siguier, F. (1946): *Sem. Hôp., Paris*, **22**, 3.
Linde, P. (1942): *Nord Med.*, **13**, 897.
*Linder, C. U., and Tyler, H. Y. (1945): *Bull. N.Y. med. Coll.*, **8**, 71.
McCullagh, E. P., and Engel, W. J. (1942): *Ann. Surg.*, **116**, 61.
*McFarland, G. E. (1951): *Ann. Surg.*, **133**, 404.
McKenna, C. M., and Hines, L. E. (1935): *J. Urol.*, **34**, 93.
Maitland, I. L.: Personal communication.
Malandra, B. (1950): *Tumori*, **24**, 332.
Manasse, P. (1893): *Virchows Arch.*, **133**, 391.
Mandeville, F. B., and Sahyoun, P. F. (1949): *J. Urol.*, **62**, 93.
Masson, P., and Martin, J. E. (1923): *Bull. Ass. franç. Cancer*, **12**, 135.
Mayo, C. H. (1927): *J. Amer. med. Ass.*, **89**, 1047.
Muntz, H. H., Ritchey, J. O., and Gatch, W. D. (1947): *Ann. intern. Med.*, **26**, 133.
*Naegeli, T. (1947): *Helv. chir. Acta*, **14**, 349.
*Nettleship, A. (1941): *J. clin. Endocrin.*, **1**, 124.
Nordmann, M., and Lebküchner, E. (1931): *Virchows Arch.*, **280**, 152.
Oberling, C., and Jung, G. (1927): *Bull. Soc. méd. Hôp. Paris*, **51**, 366.
Owen, R. A. C. (1955): *Brit. Med. J.*, **1**, 331.
*Owens, F. M. (1949): *Arch. Surg.*, **59**, 896.
*Padis, N. (1945): *Clinics*, **4**, 87.
*Palmer, R. S., and Castleman, B. (1938): *New Engl. J. Med.*, **219**, 793.
*Pantridge, J. F., and Burrows, M. McC. (1951): *Brit. med. J.*, **1**, 448.
Paul, F. (1931): *Virchows Arch.*, **282**, 256.
Peycelon, N., Miller, P., and Guillet, E. (1947): *Lyon chir.*, **42**, 291.
*Phillips, J. R. (1947): *Amer. J. Surg.*, **73**, 111.
Popken, C. (1936): *Beitr. path. Anat.*, **97**, 337.
*Pyle, F. J. (1951): *J. Urol.*, **66**, 153.
Raab, W., and Smithwick, R. H. (1949): *J. clin. Endocrin.*, **9**, 782.
Reichardt, R. (1934): *Endokrinologie*, **14**, 180.
*Rodin, F. H. (1945): *Arch. Ophthal.*, **34**, 402.
Rothernnich, N. C. (1952): *Ann. intern. Med.*, **36**, 157.
Rubin, C. B. (1929): *Arch. Path.*, **7**, 228.
Rumpel, —. (1934): *Zbl. Chir.*, **61**, 2057.
*Sachs, A., and Russum, B. C. (1936): *Nebraska med. J.*, **21**, 84.
Schroeder, K. (1928): *Virchows Arch.*, **268**, 291.
Shipley, A. M. (1929): *Ann. Surg.*, **90**, 742.
Smithwick, R. H., Greer, W. E. R., Robertson, C. W., and Wilkins, R. W. (1950): *New Engl. J. Med.*, **242**, 252.
Snyder, C. H., and Vick, E. H. (1947): *Amer. J. Dis. Child.*, **73**, 581.
Soffer, L., Mencher, W. H., and Colp., R. (1946): *Surg. Clin. N. Amer.*, **26**, 368.
*Spalding, J. M. K. (1947): *Brit. med. J.*, **1**, 564.
*Spatt, S. D., and Grayzell, D. M. (1948): *Amer. J. med. Sci.*, **216**, 39.
*Strombeck, J. P., and Hedberg, T. P. (1939): *Acta chir. scand.*, **82**, 177.
Suzuki, S. (1910): *Berl. klin. Wschr.*, **47**, 1623.
Sydnes, S. (1951): *Acta med. scand.*, **140**, 211.
*Symington, T., and Goodall, A. J. (1953): *Glasg. med. J.*, **34**, 75.
*Tenebaum, J. L. (1943): *J. Urol.*, **49**, 773.
Thorn, G. W. (1944): *Ann. intern. Med.*, **21**, 122.
*Tulloh, H. P. (1952): *Brit. med. J.*, **1**, 531.
Van Epps, E. F. (1940): *Arch. intern. Med.*, **65**, 1123.
Van Goidsenhoven, C., and Appelmans, R. (1934): *Bull. Acad. roy. Méd. Belg.*, **14**, 672.
Van Goidenshoven, C., and Appelmans, R. (1944): *Verh. vlaam. Akad. Geneesk. Belg.*, **6**, 18.
Volhard, F. (1944): *Münch. med. Wschr.*, **91**, 120.
*Walton, J. N. (1950): *Lancet*, **1**, 438.
Ward, G. E. S., Riches, E. W., and Johnson, B. (1952): *Arch. Middlesex Hosp.*, **2**, 133.
*Wells, A. H., and Boman, P. G. (1937): *J. Amer. med. Ass.*, **109**, 1176.
White, P. D. (1946): *New Engl. J. Med.*, **235**, 906.
Whiteside, M., University of Melbourne: Personal communication.
Zeckner, I. T. (1925): *Boston med. surg. J.*, **193**, 254.

* Supplemented by personal communication.

PHAEOCHROMOCYTOMA IN A PREGNANT AFRICAN WOMAN

BY

J. N. P. DAVIES, M.D.

AND

CORALIE RENDLE SHORT, M.B., Ch.M., F.R.C.O.G.

Departments of Pathology and of Obstetrics and Gynaecology
Makerere College Medical School, Kampala, Uganda

A PHAEOCHROMOCYTOMA is a tumour of chromaffin tissue which may arise in the adrenal medulla or in other sites where chromaffin tissue occurs. Many cases have been reported in recent years particularly those in which such tumours have been responsible, by the production of pressor hormones, for sustained or paroxysmal hypertension. In many cases cure after removal of the tumour has been achieved. Reviews by MacKeith (1944), Blacklock *et al.* (1947) and Graham (1951) have dealt fully with the literature.

There is some evidence to suggest that this is an uncommon tumour of negroes. In Glasgow Blacklock *et al.* (1947) recorded 1 case in 2,994 autopsies. In Mulago Hospital, Kampala, where for several years particular attention has been paid to the adrenal gland, the case here recorded is the only one encountered in 3,573 autopsies carried out since 1946. Moreover it is of interest that it occurred in a pregnant woman, and severe convulsive episodes led to a possible diagnosis of eclampsia. Although cases have been seen previously in pregnancy (Bartels and Cattell, 1950), and though in one case it caused severe hypertension in life and the patient died of profound obstetric shock (Digonnet *et al.*, 1947) we have not found in the literature available to us such a case as we record.

CASE REPORT

(53×582: P.M. 131/53.)

A primigravida of the Muzinja tribe, aged 20, at 40-weeks' gestation, was admitted to Mulago Hospital on the 29th March, 1953. She had had no antenatal care. She gave a history of having been 3 days in labour at home and she was unable to deliver herself. On examination she was rather a stout girl with no actual oedema. There was no marked anaemia. The pulse was 90, of weak volume. The pelvis appeared adequate. A macerated half-delivered foetus was found hanging out of the vulva. This was easily delivered by expression and was quickly followed by a foul-smelling decomposing placenta. Blood loss was normal. The perineum and lower part of the vagina appeared sloughing and gangrenous. The foetus was a macerated male weighing 7 pounds.

Twelve hours after delivery her condition became very poor—she was cold and clammy and developed twitching of the limbs and head followed by convulsive fits. A diagnosis of possible post-partum eclampsia was made but she died during a fit showing no response to treatment.

Autopsy was carried out within 3 hours of death. The body weighed 41·6 Kg. The brain was slightly oedematous (1700 g.) but there were no vascular lesions and no thrombus was present in the venous sinuses. The pituitary (0·6 g.) was normal. The lungs were congested and oedematous and the heart was dilated (295 g.). The liver was normal and without evidence of haemorrhagic or degenerative lesions. The right kidney showed some dilatation of the calyces but otherwise no renal lesions were observed. The uterus contained some infected blood clot and showed evidence of an early septic endometritis. The cervix had disintegrated into shaggy threads of tissue and there was sloughing of the vagina, vulva and perineum. The left adrenal (4·3 g.) was normal but the right adrenal presented as a round tumour of a purple brown colour with some normal adrenal tissue to one side (Fig. 1). The mass weighed 43 g. and on section was found to be roughly globular, about 3·5 cm. in diameter, and composed of soft brown red tissue mottled with haemorrhagic areas. It was well encapsulated being contained in the fascial capsule of the

adrenal which was stretched around it (Fig. 2). The diagnosis of phaeochromocytoma was confirmed by microscopic examination which showed the tumour to be composed of spindle-shaped or polyhedral cells with numerous multinucleate cells (Fig. 3). There were a few haemorrhagic areas but no necrosis was seen. The tumour was extremely vascular with many thin-walled blood vessels, the cells being often arranged perivascularly round these channels. There were no foamy cells and only a few cells were vacuolated. Mitoses were very few and the tumour seemed benign. As formalin fixation was used the only specific stain utilized was the Anilin blue Orange G. stain of Gomori (1946), and this revealed, both in the tumour cells and in the normal medullary cells, the presence of purple red granules. One interesting finding was the very marked hypertrophy of the muscle bundles in the wall of the adrenal vein (Fig. 2), which Dr. D. B. Allbrook estimates as being twice as great as that usually found in the adrenal veins of Africans.

No estimation was made of the hormone content of the tumour. Microscopic examination of the other organs was uninformative.

Discussion

The relationship of the phaeochromocytoma to the signs and symptoms in this case is unfortunately indefinite because of the circumstances of her admission. She died in severe shock, with no pituitary lesions, after twitchings and convulsions. We have no previous history of epilepsy and no evidence of brain damage. She had evidence of early but severe infection of the uterus and pelvic tissues but no pathological evidence of eclampsia. It is possible that the convulsions were due to the infection. Graham (1951) has recorded twitchings and convulsions as among the more uncommon symptoms of phaeochromocytoma. The picture presented by this patient is consonant with the possibility that the tumour was responsible for the symptoms.

It is interesting to consider if the tumour and its secretions had any effect upon the course of labour. Both adrenalin and nor-adrenalin are produced by phaeochromocytomas (Holton, 1949) and have different pharmacological effects (Goldenberg, Snyder and Aranow, 1951), although these have been chiefly studied in relation to the cardiovascular system. The effects of adrenalin on the uterus are confusing (Reynolds, 1949). Kaiser (1950) and Garrett (1954) have shown that in general terms adrenalin inhibits the large coordinate uterine contractions in labour and reduces the muscle tone, while nor-adrenalin stimulates the uterine muscle, increases tone and increases the frequency of contraction, though Kaiser doubts if it increases the expulsive forces. The results of giving mixtures of these hormones could therefore vary very much. Whether any hormonal effects were the basis of the failure of this woman to deliver herself cannot be ascertained, but further study of similar cases may throw light on this possibility.

Summary

A case of phaeochromocytoma in an African woman is described. She died in obstetrical shock with epileptiform convulsions at term having failed to deliver herself. This might have been due to the effects of hormones produced by the tumour.

We are grateful to Dr. D. B. Allbrook and Dr. P. B. Marshall of the Anatomy and Pharmacology Departments, Makerere College, for help in the discussion of this case.

References

Bartels, E. C., and Cattell, R. B. (1950): *Ann. Surg.*, **131**, 103.

Blacklock, J. W. S., Ferguson, J. W., Mack, W. S., Shafar, J., and Symington, T. (1947): *Brit. J. Surg.*, **35**, 179.

Digonnet, L., Thoyer Rozat, J., and Duperrat, B. (1947): *Gynéc. Obstét.*, **46**, 677. (Abstr.: *J. Obstet. Gynaec. Brit. Emp.*, 1948, **55**, 697.)

Garrett, W. J. (1954): *Lancet*, **1**, 1060.

Goldenberg, M., Snyder, C. H., and Aranow, M. (1947): *J. Amer. med. Ass.*, **135**, 971.

Gomori, G. (1946): *Amer. J. clin. Path., Tech. Sect.*, **10**, 115.

Graham, J. B. (1951): *Int. Abstr. Surg.*, **92**, 105.

Holton, P. (1949): *Nature, Lond.*, **163**, 217.

Kaiser, I. H. (1950): *Surg. Gynec. Obstet.*, **90**, 649.

MacKeith, R. (1944): *Brit. Heart J.*, **6**, 1.

Reynolds, S. R. M. (1949): *Physiology of the uterus*. 2nd ed. Hoeber, New York.

FIG. 1

The adrenal tumour showing its relation to the remaining adrenal tissue. Scale in centimetres.

FIG. 2
Showing part of the tumour and its capsule, the adrenal gland and the thickening of the adrenal. H. & E. ×6.

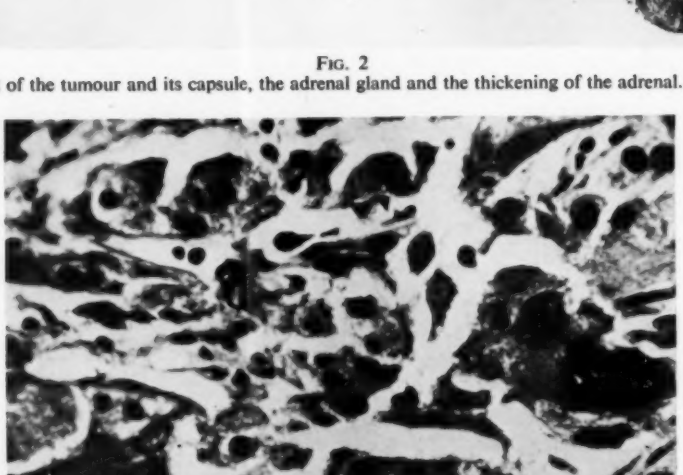


FIG. 3
Giant cells amongst the spindle cells. The sinusoidal nature of the blood vessels is also shown. H. & E. ×375.

A PRELIMINARY SERIES OF CASES OF UTERINE HYPOPLASIA TREATED BY LOCAL INJECTION OF AN OESTROGENIC EMULSION*

BY

SARA FIELD-RICHARDS, M.B., M.R.C.O.G.

Phillip Hill Clinic, Royal Northern Hospital, London

THE human uterus has been shown to be incapable of a growth-response to specific hormonal stimuli until a certain degree of differentiation has been attained in or about the third month of embryonic life (Danforth, 1939). At this stage the caudal lips of the Müllerian ducts are fusing to form the primitive uterus (Willier, 1939). The medullary region of the gonadal rudiment commences to dwindle and the cortical region is producing the hormones which will control the future destiny of the structures derived from the genital ridges (Burns, 1938). It is pertinent to note here that throughout life the vascular pattern of the uterus has a profound effect on its growth and differentiation, the rudimentary uterine structures growing along a particular vascular network laid down in the early embryonic syncytium.

Scammon (1926) has demonstrated that the uterine rudiment, which is 4–6 mm. long at the third month, undergoes growth at a uniform rate until the seventh month of pregnancy and that this rate is proportional to the pelvic and general skeletal development of the foetus. From the seventh month the uterine growth is accelerated but there is shrinkage a few days before birth with a reduction of muscular tissue. After birth uterine involution continues for about a fortnight until the organ is no larger than at the seventh month, the uterus remaining virtually unchanged until a year or two before the menarche (Scammon, 1930).

The rate of growth of the foetal uterus corresponds quite closely with the maternal rate of output of chorionic oestrogen. That this is more than coincidental is apparent in the light of further observations. There seems little doubt that the ovarian secretion of oestrogen is substantial for some time before the menses commences and that uterine growth has usually restarted by the age of 11 years, presumably under this oestrogenic influence (Parkes, 1929). This is confirmed by the fact that uterine growth can be stimulated in earlier childhood by the administration of oestrogens, the pre-pubertal organ in animals being sufficiently sensitive to render it a useful test object for the assay of oestrogens or gonadotrophins (McPhail, 1936; Freed and Soskin, 1937; Levin and Tyndale, 1937; Evans, Varney and Koch, 1941). Exogenous oestrogens have frequently been shown to be capable of causing uterine growth in immature animals (Allen and Doisy, 1927; Parkes, 1929; E. Allen, 1937; Reynolds, 1937) and in humans to reverse the atrophy following the menopause or ovariectomy (Allen and Doisy, 1927; Korenchevsky and Jones, 1947; Courrier, 1945). It has been observed in animals that the reactivity of the uterus to oestrogen varies with age (Price and Ortiz, 1944) and that the cervix of the adult rat is more sensitive to oestrogenic stimulus than it is in less mature animals (Hamilton, 1947).

In normal women the uterus shows a small degree of cyclic growth which may be related to the cyclic variation of ovarian oestrogen or to the cyclic changes in uterine vascularity—or both. In pregnancy the great increase in the size of the uterus is possibly due in large measure to the direct mechanical stimulus, the effect of enormously increased oestrogen output by the placenta being in all probability an important factor. It is worth noting the order of this uterine development in gestation. While the average weight of the uterus in the pre-menarche is

* An extract of this article was read at the International Congress of Fertility in New York, 1953.

10–15 g. and in the normal cyclic woman 50–60 g. (fluctuating by a few grammes in each cycle), the pregnant uterus weighs as much as 800–1,000 g. and after parturition never regresses to its previous size until after the menopause, when it gradually diminishes over a period of 5 years or more (Loewe, 1925).

The profound effect of the increased vascularity of the uterus upon uterine growth (Bouin and Courrier, 1929; Reynolds, 1938; MacLeod and Reynolds, 1938) must remain in the forefront of this discussion, especially as the effect of oestrogens in inducing development could easily arise from their vasodilator activity alone and not from any specific trophic effect on the myometrium. This suggests that augmented vascularity may thus increase general metabolism or bring some other special trophic agent, such as androgen, to the myometrium. Certainly oestrogens will induce uterine hyperaemia and even cervical erosion if in excess (Joachimovits, 1927; Asdell and Marshall, 1927; E. Allen, 1928; Fagin and Reynolds, 1936; Jacobsen, 1944). Various changes have been observed following oestrogen administration: first an accumulation of fluid followed by tissue-infiltration with eosinophil and macrophage cells; the pre-secretory and mitotic changes occur in the endometrial glands and epithelium within a few hours and although mitosis is not much evident in the myometrium, unless the uterus is distended, there is a marked hypertrophy of myometrial cells (W. M. Allen, 1937). The cervical mucus becomes glairy or transparent and copious (Pommerenke and Viergiver, 1946) and the reticular connective tissue becomes collagenous.

The condition in the adult described as uterine hypoplasia, or so-called infantilism, is commonly brought to light as a result of the patient complaining of infertility, although menstrual disorders ranging from amenorrhoea to menorrhagia may be presenting symptoms. The size of the uterus is generally below normal but especially characteristic is the disproportionately long cervix (Danforth, 1939) which is narrow, of poor vascularity and frequently has the so-called "pin hole os". There is, furthermore, a high incidence of retroflexion and acute anteflexion in these cases (Jarcho, 1946) and a shallow vaginal fornix is often seen. Bourne (1947) postulates that the cause of infertility in these cases is an associated failure of ovulation, since maldevelopment does not prevent nidation.

The cause of uterine hypoplasia is far from evident. While a great deal of work has been done which indicates that oestrogens are the promoters of normal uterine growth, it is not yet clearly established that hormones are the missing factor in the disordered development. There are many hypoplastic uteri in which the endometrium is responding to endogenous ovarian hormones, as shown by normal and regular menstruation (Jarcho, 1946; Clauberg, 1934; Moricard, 1936; W. M. Allen, 1932; Courrier and Kehl, 1930). In such cases it may be that there is a deficiency of oestrogen which nevertheless does not disturb the endometrial cycle because of a lower threshold of response, or it may be that the myometrium is in some way prevented from responding to a normal oestrogen output.

The nature of such an inhibition is obscure. It may originate in the receptor failure of the individual muscle fibres themselves; in the production of antibodies in the uterus; in an inadequacy of vascular supply to the myometrium or in some irregularity of oestrogen metabolism arising in the liver or perhaps in the endometrial glands, where it is now believed that oestriol is normally formed as a metabolite of the ovarian oestradiol. The last possibility presupposes that the oestrogenic stimulus required for endometrial proliferation is qualitatively different from that needed for general uterine maturation. It is noteworthy in this connexion that in rats testosterone appears capable of counterbalancing oestrogen in its endometrial effect (Wilson, Hamilton and Young, 1941) and in excess even to cause endometrial atrophy. Nevertheless some increase in the size of the uterus of experimental animals has been induced with testosterone, probably through myotrophic properties which result from inhibition of protein katabolism. In a similar way oestrogens may require the cooperation of a certain proportion of testosterone or some other hormonal agent, such as progesterone (Hisaw, Greep and Fevold, 1937a), in order to provide an optimal growth stimulus to the uterus. The part played by folic

acid in promoting oestrogenic action (Hertz and Tullner, 1949) also needs fuller elucidation.

Therapeutically, large doses of oestrogens administered to cases of uterine hypoplasia have hitherto frequently failed to produce any response (Moricard, 1936; Foss, 1938; Greene, 1946; Bourne, 1947). If indeed it is possible to overcome any inhibition to response that may be present, it is reasonable to suppose that such failures originate from one or more of the following defects in the treatment:

1. The wrong oestrogen may have been employed;
2. Some other necessary hormone may have been omitted from the treatment;
3. The oestrogen may have been administered by an inappropriate route;
4. The dosage may have been inadequate or the duration and timing of treatment may have been unsuitable;
5. The methods employed to recognize uterine development may not have been reliable.

The reasons for the methods adopted in the present study will be clarified by the discussion of all these possibilities:

1. *The Oestrogen.* Many oestrogens of both steroid and stilbene types have been employed in attempts to mature the infantile uterus in animals and humans and study of the results gives the impression that, where any success has been obtained, the hormone used has, as a rule, been closely related to the natural oestradiol (E. Allen, 1937; Parkes, 1929; Reynolds, 1937; Ferreira Gomez, 1947; Perloff, 1950). Dorfman (1937, 1940) found in obtaining responses in the infantile rat uterus that the most potent oestrogens (in decreasing order) were:

oestradiol
oestradiol monobenzoate
oestrone
equilin
equilenin
oestrone benzoate
oestriol.

Oestradiol is ideal for administration as a subcutaneous implant and could be employed if this method of treatment with very slow absorption could be made practicable (Perloff, 1950; Greenblatt and Suran, 1949).

Oestradiol monobenzoate or oestradiol diproprionate are slowly absorbed from oily solution after intramuscular injection and for this purpose are to be preferred to the unesterified form. As an even slower absorption of oestradiol monobenzoate can be obtained from an aqueous emulsion of this hormone (Lens, Overbeek and Polderman, 1949). Such a preparation for parenteral use was made available for this experiment by Messrs. Organon Laboratories Limited.

Ethinyl oestradiol is the most potent known oestrogen but it is principally noted for its activity by mouth, by which route it is eliminated from the body within 24 hours. No longer-acting preparation of this hormone is yet available but its oral use has occasionally been reported as being very effective in cases of hyperplasia with amenorrhoea (Birnberg *et al.*, 1947; Hoffmann, 1949).

2. *Other Necessary Hormones.* Very little work has been done in which oestrogens and other hormones have been combined in an attempt to produce a uterine growth response and any remarks on the subject must be of a conjectural nature. Pituitary growth hormone, thyrotrophin and gonadotrophin, thyroid hormone, testosterone and progesterone are among the hormones which may partake in this effect.

It has been demonstrated that testosterone in various forms has an effect in causing increase in uterine weight and vascularity in rats (Korenchevsky and Hall, 1937; Aschheim and Varangot, 1939). This may be on account of the water and protein-retaining properties of this hormone, resulting in an increase of myometrial tissue. It is perhaps significant that the ovary produces both oestrogen and testosterone and that very evident synergism exists between the two hormones in many respects. On the other hand, it is established that they have contrary effects upon the endometrium, for the haemostatic action of testosterone is a styptic one upon the spiral arteries, while that of oestrogen is due to a renewal of proliferative stimulus preventing endometrial breakdown.

Progesterone has been shown to have synergism with oestrogens in bringing about the endometrial secretory phase but no such effect is known on the general growth of the uterus, although this has been surmised (Hisaw, Greep and Fevold, 1937b). The cyclic increase in

uterine weight is likely to be due to the menstrual effect alone and is in any case rapidly reversed. Furthermore, it has never been shown that there is any correlation between uterine hypoplasia and anovulation, in which it may be presumed that very little, if any, progesterone is produced.

The relationships between the anterior pituitary hormones, the thyroid hormones and the oestrogens are undoubtedly of great complexity but there has never emerged any clear indication that uterine development depends on any except the oestrogenic hormones themselves.

3. *Route of Administration.* It will be apparent from the foregoing that defect of the vascular supply to the uterus may well be the cause or a contributory cause of hypoplasia. It follows that the best chance of success with oestrogen therapy is likely to attend local administration of the hormone into the uterus wall itself (Bouin and Courrier, 1929; Buchheim and Zaleski, 1930). It seems, however, that this perhaps fundamental aspect of treatment has been overlooked in almost all previous work on this subject. Ferreira Gomez (1947) did, however, employ a method of injection of oestradiol monobenzoate into the uterine wall and obtained some promising results. In rabbits he observed that the uterine cornu which was injected increased in size more than the rest of the organ and that the overall uterine growth was comparable to that induced by about 50 times as much of the oestrogen given by ordinary intramuscular injection. Both of these observations stress the importance of the local treatment as there is a marked maximal effect at the site of administration. This author also found that in his clinical group local introduction of oestrogen bougies was as satisfactory as the injection and much more convenient, since his original method involved a daily injection into the uterine wall.

It was part of the intention in the present work to test this principle further and to improve upon the method by the use of long-acting preparations of oestrogen and by spacing the dosage so as to simulate as far as possible the normal cyclic peaks of oestrogen production. It seemed, moreover, that it was important to limit the number of oestrogenic applications, in view of the likelihood of the occurrence of cervical erosion.

Long-acting forms of oestradiol which appeared suitable for overcoming these difficulties were:

(1) Fused pellets of oestradiol introduced into the uterine lumen.

(2) Emulsions of oestradiol monobenzoate injected into the cervix.

4. *Dosage.* Failure to induce growth of the infantile uterus with oestrogens has sometimes been due to overdosage. That a high concentration of oestrogen is needed at the organ-site itself is suggested by the frequent absence of myometrial development, despite a cyclic endometrium and also by the rather frequent lack of success when oestrogens are given systematically, even when the dose is large by normal standards. It has been maintained by several authorities (Asdell and Marshall, 1927; Laqueur and de Jongh, 1928; Laqueur, Hart, de Jongh and Wijsenbeek, 1925) that repeated small daily doses have more uterotrophic effect than infrequent large doses. This statement must be qualified since it is certain that the effects of the large doses concerned were of a relatively short duration, intramuscular oestradiol monobenzoate in oil being excreted in 3 or 4 days.

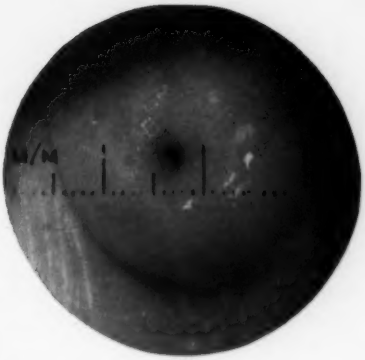
It has been reported that in animals uterine response to oestrogens is exhausted in a few months (Engle and Smith, 1935; Selye, Thomson and Collip, 1935; Reynolds, 1935; McEuen, 1936) and further that the optimal influence of oestrogenic treatment upon the uterus is attained by treatment only lasting 2 to 4 weeks (Zuckerman, 1937). This should not be unexpected, since the normal cyclic oestrogenic stimulus to the uterus is diminished from about the 26th to the 4th day of the cycle and this certainly suggests that a constant high dosage administration may be inadvisable and wasteful. It is also much more likely that such a regimen will interfere with menstrual rhythm.

On the basis of this, it appears rational to use either small daily doses of oestrogen in fortnightly courses, preferably once every cycle, or more conveniently to give a single monthly administration of a longer-acting preparation aimed at giving a small daily uptake for upwards of 2 weeks. This latter technique has been

Case 1

(*a*)

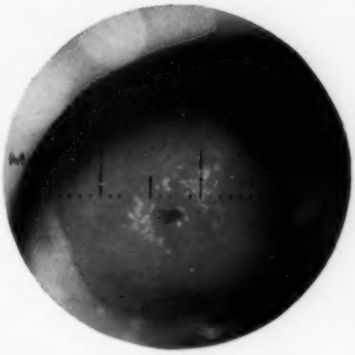
(*a*) Typical hypoplastic cervix with small external os. Patient married 10 years. Extensive investigations elsewhere.



(*b*)

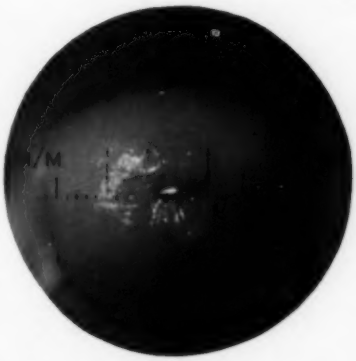
(*b*) After 4 injections. Marked general development. Cascading clean cervical plug. Conception 3 months later.

Case 2



(*a*)

(*a*) Typical hypoplasia. Small os. Central erosion and no mucous plug.



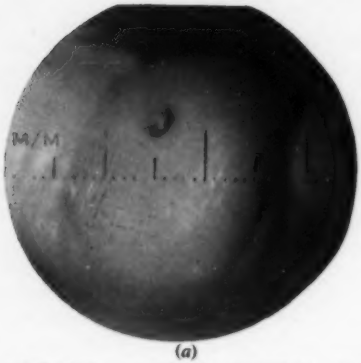
(*b*)

(*b*) After one injection—generalized increase in size with typical extension of erosion. Improved mucous plug.

(*c*)

(*c*) After 2 injections. Cervix normal in size. Mucous plug clean and cascading. Conception occurred within 2 months.

Case 3



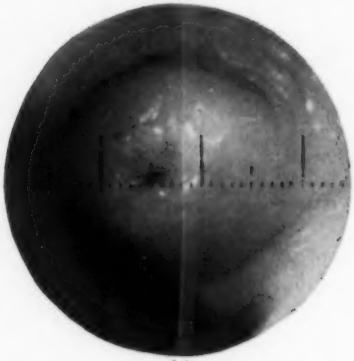
(*a*)

(*a*) Typical generalized hypoplasia and retroversion.

(*b*)

(*b*) After 3 injections. Showing striking cervical development and clear mucous plug. Conception occurred during the next cycle.

Case 4



(*a*)

(*a*) Typical cervix with pinhole os.

(*b*)

(*b*) After 2 injections. Marked increase in development, with a superficial non-infected "erosion".

(*c*)

(*c*) After 1 month with no treatment. Development improved but "erosion" more extensive. Electrocautery healed erosion, and patient conceived 6 months later.

previously reported in the treatment of uterine hypoplasia (Friedberg, 1951) and it would appear that a more adequate trial of this method would be a useful contribution, both to the treatment of the condition and to the evaluation of the aqueous emulsion as a medium.

There remains the question of the optimal dose per injection and this may certainly vary from case to case. Jeffcoate (1939) indicated the uselessness of oestrogen therapy in gross hypoplasia, although he reports a useful improvement in cases of more moderate degree. In the present series dosage cannot be clearly established until the propensities of the emulsion have been further investigated. Since it was planned to use the injection locally and since the absorption was expected to be prolonged over 2 to 3 weeks (Lens, Overbeek and Polderman, 1949), the dosages suggested were based on those used with implanted oestradiol (Perloff, 1950), rather than those usually employed for oestradiol monobenzoate by the intramuscular route (Zondek, 1934; Clauberg, 1933; Marlow, 1936). The emulsion available contained 10 mg. of oestradiol monobenzoate per ml. and it was thought likely that 1 ml. per month of this might be an effective dose.

In the light of the foregoing information, it is submitted that maximal effects in maturing the infantile uterus might be expected if the following technique were employed:

(*a*) Local injection of oestradiol monobenzoate into the cervix uteri;
(*b*) Use of an aqueous emulsion of the hormone, which is expected to have an active duration of 2 to 3 weeks;
(*c*) Injection of 10 mg. (1 ml.) once monthly, near the commencement of each menstrual cycle, if one exists.

5. *Assessment of Uterine Development.* These are:

(*a*) The overall length, breadth and depth;
(*b*) The internal length;
(*c*) The ratio of the length of the body of the uterus to the length of the cervix; one-half of this value is termed the uterine index (Meaker, 1934; Meigs, 1939);
(*d*) The size and appearance of the os uteri and cervix as seen *per vaginam*;
(*e*) The incidence of retroflexion and acute anteflexion;
(*f*) The weight of the organ.

(*a*) The overall size of the organ can be roughly estimated by bimanual examination. This is subject to errors due to malformations of the uterus, to subcutaneous fat or to loaded bladder or bowel, as well as to personal errors arising from the method and impressions of the examiner. The resultant opinion is no more than helpful as a corroboration of other more accurate determinations (Russell, 1945).

The size can also be approximately gauged by comparative X-ray shadows (Bourne, 1947) but, as this is arduous, difficult to standardize and subject to error through malformations of the organ, it was decided that this method was not sufficiently important to justify the use of expensive X-ray films.

(*b*) The internal length of the lumen can be measured by means of a sound introduced through the os uteri to the fundus. For this purpose it is necessary to straighten out, as far as possible, a retroflexed or anteflexed organ for the reading to be taken and also to devise a means of marking the position of the external os on the sound. This measurement is simple and reasonably accurate but is troublesome as some very hypoplastic organs tend to be long and narrow.

(*c*) According to Meaker (1934), an infantile organ exists if the uterine index (one-half the ratio of the body-length to the cervix-length) is less than 0·75. This index is a valuable estimate of the degree of development but up to now no valid method of determination has been described.

In the United States an hysterometer is employed for this measurement. This graduated uterine sound is introduced to the cervical canal. When the point is felt to pass the internal os, a note is taken of the length. The instrument is then introduced further, until the fundus is reached. This gives the total length of the organ and that of the body alone can thus be calculated by deducting the length of the cervix from the total length.

Experience with uterine sounds suggests to the present writer that this method of estimating the position of the internal os is so subject to

error that the method is rendered valueless. An error of 1 cm. could easily be made and this error would be magnified in calculating the index: e.g., suppose the uterus to be measured has an internal length of 6 cm. and the cervical canal is 3 cm. long, then the uterine index will be:

$1/2 \times 3/3 = 0 \cdot 5$ *which is a hypoplastic measurement.*

If an error of 1 cm. be made in the cervical measurement, making it 2 cm. long, the result will be:

$1/2 \times 4/2 = 1 \cdot 0$ *which is a fully adult measurement.*

(*d*) The size of the cervix as seen *per vaginam* is an indication of the general development of the organ and is of value as a diagnostic guide, especially if considered in conjunction with its general vascularity and with the size of the external os. The absence of a clear, cascading cervical plug and the presence of shallow vaginal fornices afford further confirmation of the diagnosis.

By standardizing the position of photographs of the cervix it was possible to assess the development of the cervix with some degree of accuracy.

(*e*) Retroflexion is a common accompaniment of the hypoplastic uterus. It is, moreover, easily demonstrated.

(*f*) No practicable method of gauging the weight of the uterus *in vivo* has been suggested.

In much of the previous work on this subject, in which there appear claims of considerable uterine development resulting from oestrogen therapy, the striking absence of details concerning these important and difficult measurements does nothing to dispel the scepticism of the many who have failed to discern any maturation from similar treatment. It is hoped that this admission of the difficulties involved will encourage acceptance of the data which are here presented.

The uterine index was considered important but not capable of accurate measurement and the cases investigated were assessed mainly from the size and appearance of the external os and cervix, from the internal length of the organ and from the impressions gained from bimanual examination.

Material Used. An emulsion of oestradiol benzoate, 10 mg. in a 1 ml. ampoule, was the standard dose, except in those cases where a superficial erosion was either present at the time of examination or developed later.

In these cases 5 mg. was the selected dose. In one instance only there was an extension of the eroded area, which healed after cessation of treatment.

Administration. The emulsion was drawn up into a glass syringe and a specially toughened fine bore (No. 12) needle with a 5-inch shaft was used. With a light volsellum the cervix was pulled gently downwards. The emulsion was injected at about $\frac{1}{2}$ to 1 inch to the side of the canal of the cervix, directing the needle slightly inwards in order to allow for any displacement of tissue. In the case of the small, tough cervix, it was sometimes difficult to introduce the whole dose. This problem was, however, usually overcome after one or two treatments as the resulting hyperaemia made the absorption easy.

Measurements. The question of accurate measurement in these cases presented one of the chief problems, as it was decided that the margin of error, using a hysterometer, was too wide. After due consideration it was thought that the best method was to pull the cervix downwards in the long axis of the vagina, endeavouring to make the alignment of cervix and fundus as continuous as possible. A soft metal sound, with a piece of rubber tubing on the shaft, was introduced through the cervical canal until the tip was felt to reach the top of the cavity. The tubing was then gently pushed upward until it rested against the external os and it was then fixed with an artery forceps and the sound withdrawn. A measurement was taken at each visit between the tip of the sound and the distal end of the rubber tubing, the result being recorded in centimetres.

It will readily be appreciated that such a method must of necessity be open to some error. The impression was that the method would serve as a guide to the proportionate increase in size, even if the exact amount was not determined.

Results

In view of the problems arising from the relative measurements obtainable, a series of controls was used. It was seen from these figures

that a slight but definite increase during the premenstrual phase in many instances occurred but the average weekly variation was slight, bearing in mind the method used. The average variation in length was 0·32 cm. in the whole series, whereas in the treated cases it was in the neighbourhood of 0·8–0·9 cm. a significant increase.

It was only possible to obtain 10 control cases in this instance, owing to the difficulty of persuading the busy housewife to attend weekly over a period of 3 months.

In this series an average number of 4 injections was given as it was found that, if the response was not immediate and progressive, treatment would prove disappointing.

In the 30 cases the maximum increase in length was 2·2 cm.

In the 30 cases the minimum increase in length was 0·4 cm., giving an average of 0·944 cm.

The most striking feature, the increase in cervical development, was shown by the colour photographs which were all taken at mid-cycle. In many instances even a very poorly developed cervix showed a small but clear mucous plug.

In several cases a very severe erosion developed, associated with the treatment and it was found necessary to suspend the injections and treat the cervix by electric cautery. In one instance conception occurred 6 months after healing.

It was also noted that there was a marked increase in tubal tone, as shown by improved peristalsis, demonstrated by the Sharman Insufflator.

An interesting point is that in no case was the menstrual rhythm disturbed. Table I shows the results in relation to subsequent pregnancy.

Conclusion

It is not possible to conclude from 30 cases that the results obtained could be repeated on a much larger series of cases. Nor is it easy to estimate the proportion of successfully treated cases of infertility due to hypoplastic uterus by other means. In this series it has been proved that most of the cases treated did respond to the treatment by uterine growth and in a gratifyingly high proportion of cases by pregnancy.

Abortion in one or more cases before carrying to term is a common occurrence and may be regarded as evidence of increasing uterine maturation.

Full-time pregnancy in 50 per cent of the cases must be regarded with some satisfaction and has been proved of statistical significance.

Addendum: Statistical Analysis

(1) *Comparison of 86 hypoplastic cases receiving no treatment with 30 hypoplastic cases receiving emulsion*

	Cases	Conception	Proportion
No treatment	86	10	·1163
Emulsion	30	24	·80
	116	34	

$$p = \frac{34}{116} = \cdot 2931$$

Standard error of difference in proportion

$$= \sqrt{\cdot 29 \times \cdot 75 \left(\frac{1}{86} + \frac{1}{30} \right)}$$

$$= \sqrt{\cdot 2175 \times \cdot 0449}$$

$$= \underline{\underline{\cdot 09766}}$$

Actual difference in proportion = ·80 − ·1163
= ·6837
= 7·67 × Standard Error

i.e., the proportion conceiving is significantly higher for the group treated with emulsion.

Table I

		Conception		Live Births		Failures	
		No.	Per cent	No.	Per cent	No.	Per cent
No Treatment	(86)	10	11·6	8	9·3	76	88·4
Oral Oestrogen	(39)	9	23·1	6	15·4	30	74·4
Intra-uterine Implant	(15)	—	—	—	—	15	100
Oestradiol Emulsion	(30)	24	80	15	50	6	20

(2) *Comparison of 86 hypoplastic cases receiving no treatment with 39 cases receiving stilboestrol*

	Cases	Conceptions	Proportion
No treatment	86	10	·1163
Stilboestrol	39	9	·2565
	125	19	

$$p = \frac{19}{125} = \cdot 152$$

Standard error of difference in proportions

$$= \sqrt{\cdot 152 \times \cdot 848 \left(\frac{1}{86} + \frac{1}{39}\right)}$$

$$= \sqrt{\cdot 1289 \times \cdot 0372}$$

$$= \cdot 06925$$

Actual difference in proportions = ·2565 − ·1163
= ·1402
= 2·0 × Standard Error

i.e., the proportion conceiving is not significantly higher for the group treated with stilboestrol.

ACKNOWLEDGMENTS

I would like to express my appreciation to Mr. Lane Roberts and Dr. Raymond Greene for their help and encouragement.

REFERENCES

Allen, E. (1928): *Amer. J. Anat.*, **42**, 467.
Allen, E. (1937): *Cold Spr. Harb. Symp. quant. Biol.*, **5**, 104.
Allen, E., and Doisy, E. A. (1927): *Physiol. Rev.*, **7**, 600.
Allen, W. M. (1932): *Amer. J. Physiol.*, **100**, 650.
Allen, W. M. (1937): *Cold Spr. Harb. Symp. quant. Biol.*, **5**, 66.
Aschheim, S., and Varangot, J. (1939): *C. R. Soc. Biol., Paris*, **130**, 830.
Asdell, S. A., and Marshall, F. H. A. (1927): *Proc. roy. Soc., B.*, **101**, 185.
Birnberg, C. H., Livingston, S. H., Kurzrok, L., and Sherber, D. A. (1947): *Amer. J. Obstet. Gynec.*, **54**, 855.
Bouin, P., and Courrier, R. (1929): *Arch. Anat. micr.*, **25**, 189.
Bourne, A. (1947): *Brit. med. J.*, **1**, 79.
Buchheim, W., and Zaleski, W. (1930): *C. R. Soc. Biol., Paris*, **104**, 896.
Burns, R. K., jr. (1938): *Amer. Nat.*, **72**, 207.
Clauberg, C. (1933): *Zbl. Gynäk.*, **57**, 1991.
Clauberg, C. (1934): *Z. Geburtsh. Gynäk.*, **107**, 331.
Courrier, R. (1945): *Endocrinologie de la Gestation.* Masson, Paris.
Courrier, R., and Kehl, R. (1930): *Proc. 2nd Int. Congr. Sex. Res.*, 357.
Danforth, C. H. (1939) *in* Allen, E. (ed.): *Sex and Internal Secretions.* 2nd edition. Williams and Wilkins, Baltimore. p. 328.
Dorfman, R. I. (1937): *Proc. Amer. Soc. biol. Chem.*, **31**, xxiv.
Dorfman, R. I. (1940): *Proc. Soc. exp. Biol., N.Y.*, **45**, 594.
Engle, E. T., and Smith, P. E. (1935): *Anat. Rec.*, **61**, 471.
Evans, J. S., Varney, R. F., and Koch, F. C. (1941): *Endocrinology*, **28**, 747.
Fagin, J., and Reynolds, S. R. M. (1936): *Amer. J. Physiol.*, **117**, 86.
Ferreira Gomez, A. (1947): *Rev. esp. Obstet. Ginec.*, **6**, 81, 185, 273, 339.
Foss, G. L. (1938): *J. Obstet. Gynaec. Brit. Emp.*, **45**, 74.
Freed, S. C., and Soskin, S. (1937): *Endocrinology*, **21**, 599.
Friedberg, V. (1951): *Geburtsh. u. Frauenheilk.*, **11**, 923.
Greenblatt, R. B., and Suran, R. S. (1949): *Amer. J. Obstet. Gynec.*, **57**, 294.
Greene, R. (1946): *Brit. med. J.*, **1**, 9.
Hamilton, C. E. (1947): *Anat. Rec.*, **97**, 47.
Hertz, R., and Tullner, W. W. (1949): *Endocrinology*, **44**, 278.
Hisaw, F. L., Greep, R. O., and Fevold, H. L. (1937a): *Proc. Soc. exp. Biol., N.Y.*, **36**, 840.
Hisaw, F. L., Greep, R. O., and Fevold, H. L. (1937b): *Amer. J. Anat.*, **61**, 483.
Hoffman, F. (1949): *Geburtsh. u. Frauenheilk.*, **9**, 778.
Jacobsen, E. M. (1944): *Endocrinology*, **34**, 376.
Jarcho, J. (1946): *Amer. J. Surg.*, **71**, 106.
Jeffcoate, T. N. A. (1939): *Brit. med. J.*, **2**, 671.
Joachimovits, R. (1927): *Arch. Gynäk.*, **131**, 86.
Korenchevsky, V., and Hall, K. (1937): *J. Path. Bact.*, **45**, 681.
Korenchevsky, V., and Jones, V. E. (1947): *J. Geront.*, **2**, 116.
Laqueur, E., and De Jongh, S. (1928): *J. Amer. med. Ass.*, **91**, 1169.
Laqueur, E., Hart, P., De Jongh, S., and Wijsenbeek, I. A. (1925): *Dtsch. med. Wschr.*, **52**, 4.
Lens, J., Overbeek, G. A., and Polderman, J. (1949): *Acta Endocr. (Kbh.)*, **2**, 396.
Levin, L., and Tyndale, H. H. (1937): *Endocrinology*, **21**, 619.
Loewe, S. (1925): *Handb. norm. path. Physiol.*, **14**, 501.
McEuen, C. S. (1936): *Amer. J. Cancer*, **27**, 91.
MacLeod, J., and Reynolds, S. R. M. (1938): *Proc. Soc. exp. Biol., N.Y.*, **37**, 666.
McPhail, M. K. (1936): *Quart. J. Pharm.*, **9**, 672.
Marlow, H. W. (1936): *Science*, **84**, 377.
Meaker, S. R. (1934): *Human Sterility.* Williams and Wilkins, Baltimore.
Meigs, J. V. (1939): *Amer. J. Obstet. Gynec.*, **38**, 161.
Moricard, R. (1936): *Bull. Soc. Gynéc., Paris*, **25**, 533.

Parkes, A. S. (1929): *The Internal Secretions of the Ovary*. Longmans, New York.

Perloff, W. H. (1950): *J. clin. Endocrin.*, **10**, 447.

Pommerenke, W. T., and Viergiver, E. (1946): *J. clin. Endocrin.*, **6**, 99.

Price, D., and Ortiz, E. (1944): *Endocrinology*, **34**, 215.

Reynolds, S. R. M. (1935): *Anat. Rec.*, **62**, 269.

Reynolds, S. R. M. (1937): *Cold Spr. Harb. Symp. quant. Biol.*, **5**, 84.

Reynolds, S. R. M. (1938): *Amer. J. Obstet. Gynec.*, **36**, 437.

Russell, C. S. (1945): *Biometrika*, **33**, 213.

Scammon, R. E. (1926): *Proc. Soc. exp. Biol., N.Y.*, **23**, 687.

Scammon, R. E. (1930): *Proc. 2nd Int. Congr. Sex. Res.*, 118.

Selye, H., Thomson, D. L., and Collip, J. B. (1935): *Nature, Lond.*, **135**, 65.

Willier, B. H. (1939) *in* Allen, E. (ed.): *Sex and Internal Secretions*. 2nd edition. Williams and Wilkins, Baltimore. p. 64.

Wilson, J. G., Hamilton, J. B., and Young, W. C. (1941): *Endocrinology*, **29**, 784.

Zondek, B. (1934): *Nature, Lond.*, **133**, 209, 494.

Zuckerman, S. (1937): *Lancet*, **1**, 435.

SALPINGECTOMY OR SALPINGO-OÖPHORECTOMY?

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S.E., F.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Liverpool

CONSERVATISM is the aim when operating on a young woman suffering from a non-malignant condition. If the uterus has to be sacrificed ovarian function is preserved if possible. When both tubes are diseased at least one ovary and sometimes the uterus are saved. When only one tube has to be sacrificed the young gynaecologist is taught to conserve the ovary on that side as well as on the other side and, with this in mind, to divide the mesosalpinx close to the tube to avoid damaging the blood supply of the ovary. Thus, in the treatment of tubal pregnancy, salpingectomy rather than salpingo-oöphorectomy is usually advocated and practised.

In operating on the appendage, however, some thought is necessary as to the object of conservatism in the particular case. If the object is to preserve ovarian tissue because of its endocrine function then clearly the more that can be saved, the better. Sometimes, however, the primary object is to preserve reproductive function and, when it is, the operator might well pause to consider whether a more radical operation is preferable. Tubal pregnancy provides the best example, although the argument might well apply to a few cases of chronic salpingitis in which one tube is open (or opened) and the other is beyond hope.

When the diseased tube is removed and the patient left with one functional tube and two ovaries what are her chances of pregnancy? One ovum is liberated from one or other ovary every 28 days and, during the course of time, the probability is that each ovary will produce an approximately equal number of ova, although not necessarily at equally spaced intervals. However, for the sake of argument let it be assumed that there are 13 ovarian cycles a year, one of which is anovular. The average number of ova shed by each ovary in any one year is then 6. The ova produced on the side without an oviduct will generally be lost, although very occasionally one may successfully migrate to the tube on the other side. Nevertheless, for all practical purposes, there will be only 6 ova which can possibly be exposed to spermatozoa in the tube during the year.

If, on the other hand, the patient with unilateral tubal disease has both the tube and ovary of the affected side removed then, according to the present concept of pituitary ovarian relations, the one remaining ovary is called upon to furnish all the ova during the ensuing years. This means that all 12 ova liberated during a year will have an oviduct at hand, and the chances of pregnancy will be approximately twice as many as in the case where both ovaries are conserved.

This may be held to be a theoretical argument, but it is one which is so difficult to refute that it appears to deserve a place among the factors which need to be considered when the extent of an operation is decided. Proof of its validity would require a prolonged follow up of large numbers of women to see if subsequent fertility varies according to the type of operation carried out for ectopic pregnancy—a project which abounds in practical difficulties.

It is not suggested that one ovary should always be sacrificed; every case needs to be judged according to the needs of the patient. Moreover, it has to be recognized that if an ovary is removed it involves taking the risk of the other becoming diseased and having to be removed at a later date. Nevertheless, it may be considered that this risk is so small that it would willingly be accepted by most subfertile young women if it offered them better chances of pregnancy. The problem only arises when a woman is left with only one functional tube and where the need is to provide it with as many ova

as possible, but this is a situation which arises sufficiently often to justify giving some thought to its management.

It may be added that similar considerations arise in other connexions. For example, according to this argument, the woman with a unicornute uterus should be more fertile if she has only one ovary (on the side of the single tube) than if she has two. Again, the woman with a septate vagina and uterus didelphys or pseudodidelphys is likely to double her chances of conception by having the septum removed. Otherwise, even if both halves of the vagina can be used for coitus, impregnation ordinarily depends on choosing the Müllerian duct destined to receive the ovum during a particular fertile period.

Conservatism in surgery is commendable, but it nevertheless needs to be rational and to be adopted to serve a purpose in a particular case rather than to satisfy a principle. Casual discussion with colleagues has revealed an unawareness of the implications of salpingectomy as opposed to salpingo-oöphorectomy, and for this reason the above argument appears to warrant ventilation. And the conclusion may be that it sometimes pays to put all the eggs into one basket.

TRENDS IN THE RISKS OF CHILDBEARING AND IN THE MORTALITIES OF INFANTS DURING THE LAST 30 YEARS*

BY

CHARLOTTE A. DOUGLAS, *O.B.E.*, M.D., D.P.H., F.R.C.O.G.

Medical Officer for Maternity and Child Welfare to the Department of Health for Scotland

THIS paper deals with the trends in Scotland of the Maternal Mortality, Stillbirth, Neonatal and Infant Death rates during the last 30 years. By their review it aims to depict the present position and to indicate where improvement is still necessary. By analyzing both the total and individual death rates for mother and child it reveals the character, extent and rate of occurrence of the changes which have taken place.

At various times during the period under review—chiefly from 1911 to the present time—the classification of maternal deaths has been subjected to alterations which tend to make yearly comparisons fluctuate in a way which may have little actual relevance to the yearly course of events. Further, the actual number of maternal deaths is small numerically and is also subject to chance fluctuations; hence a long enough period has been taken to show genuine trends. The following factors cause these difficulties in classification, viz.:

1. The decennial revision of the International List of causes of death.
2. Since the Stillbirths Registration (Scotland) Act of 1938, the Maternal Mortality rates have been stated more accurately on the basis of total births. In this present study, however, the death rates have been taken from calculations made by Dr. McKinlay (Medical Statistician to the Department of Health for Scotland) on the basis of live births so that the years before and after 1939 can be compared.
3. There is the difficulty in assessment which may arise where two or more causes are stated on the death certificate.
4. The final result to a great extent depends on the accuracy of certification.

MATERNAL MORTALITY RATE

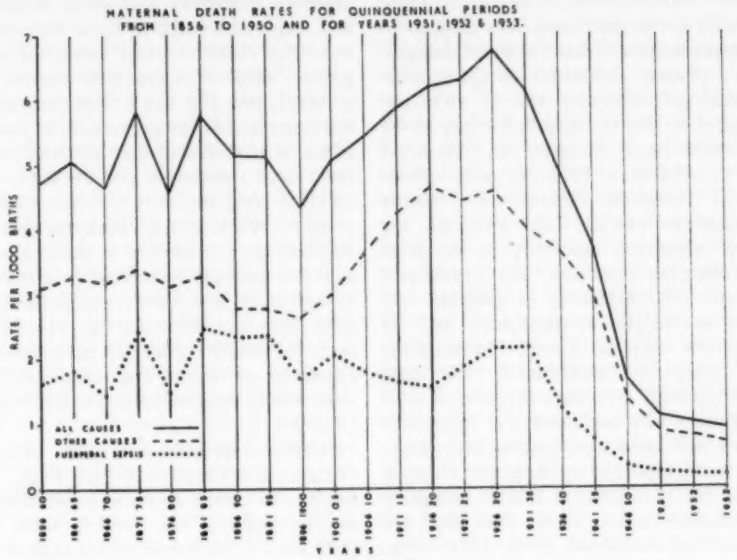
Graph 1

The first graph shows the maternal death rates for quinquennial periods from 1856 to 1950 and for the years 1951 and 1952 and 1953. It also shows the maternal death rate divided into the two broad groups of "Puerperal Sepsis" and "Other Causes of Death". Before the beginning of the century the fluctuations in the death rate were mainly accounted for by variations in the rate of Puerperal Sepsis which was presumably affected by the intensity of community septic diseases, such as scarlet fever, erysipelas, etc.; meantime the rate for Other Causes of Death tended to decline gently. From the beginning of the present century the maternal death rate started to rise very considerably and that rise continued until 1920 and was entirely due to the rise in the rate for Other Causes of Death. From 1920 this rate remained steady for a decade while the further rise in the total rate was due entirely to a rise in the rate of Puerperal Sepsis. In 1930 the rate for Other Causes started to fall and the rate for Puerperal Sepsis began to decline shortly afterwards since when both rates have fallen rapidly to their present level of 0·9 per 1,000 births.

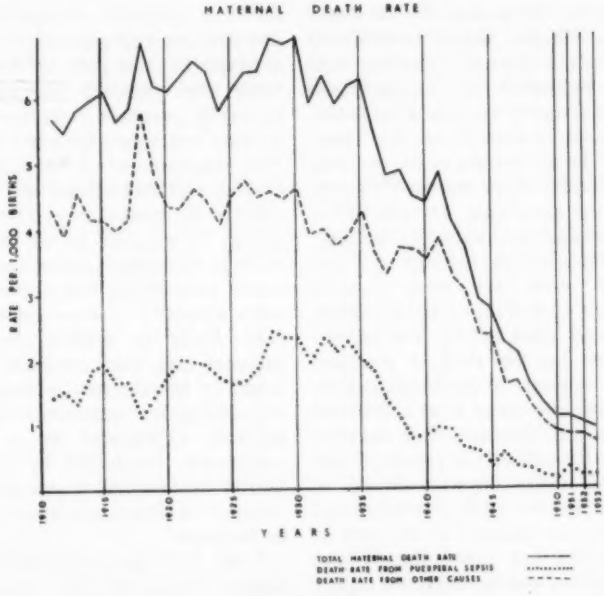
Graph 2

Graph 2 shows the picture in yearly detail from 1911 to date and demonstrates that the fall which began in 1931 was chiefly due to the fall in Other Causes of Death. The Puerperal Sepsis rate began to fall steeply in 1934 and this sharp fall continued until 1939 when, after a

* Read at a Meeting of the Edinburgh Obstetrical Society on 11th November, 1953.


MATERNAL DEATH RATES FOR QUINQUENNIAL PERIODS
FROM 1856 TO 1950 AND FOR YEARS 1951, 1952 & 1953.
RATE PER 1,000 BIRTHS
ALL CAUSES
OTHER CAUSES
PUERPERAL SEPSIS
YEARS

GRAPH 1



GRAPH 2

slight rise in 1940 and 1941, it continued more gradually until the present time. It is difficult to give exact explanations of many of those changes. There was a gradual awakening to the seriousness of Maternal Mortality and in 1928 the Scottish Board of Health published a Report by Kinloch, Smith and Stephen on Maternal Mortality in Aberdeen 1918–27, with special reference to Puerperal Sepsis. This report focused attention on the fact that in the majority of infections, especially in the fatal ones, the infecting organism was introduced from without. The organism responsible was usually the haemolytic streptococcus and its relationship to Scarlet Fever, Mastoiditis, Erysipelas, etc., was established. The part played by attendants who were carriers, or who had sore throats was explained and from that time the now well-known methods of prevention developed. In the report of the Registrar General for Scotland for 1947 there is a table compiled by Dr. McKinlay which shows that the case fatality rate had increased until 1928, after which it began to drop although the notification rate continued to increase until 1934. In that same year, however, the decline in the death rate from Puerperal Sepsis began. In 1930 the Interim Report on Maternal Mortality and Morbidity was published by Dame Janet Campbell and this certainly awakened the public conscience, although obstetricians had been fully conscious of the seriousness of the problem for some time. Various other reports followed, more or less on the same lines. In spite of increasing obstetrical and local authority concern, little real effect was made on the rate of Other Causes of Death until 1941, when a rapid improvement began. One of the probable reasons for this began many years before. The recruitment examinations for the 1914–18 war had aroused national interest in the physical condition of the people and many local authorities had begun to turn their attention from environmental hygiene to the care of the person. It was soon realized that many physical defects of adult life had their roots in early childhood and thought, therefore, was directed to the care of the infant and child and this naturally was extended to the mother and her influence on her unborn babe. Local authorities began to establish maternity and child welfare schemes and important items in these were home visitation and children's and antenatal clinics. The general care of prospective mothers and their children, plus the newly acquired knowledge of the cause and of the prevention of rickets had its effect. It is probable that much of the intensive care, both preventive and curative, devoted to children from the early nineteen twenties began to show effects on the Maternal Mortality rate 20 years later, evidenced in the gradual decrease in pelvic and other skeletal abnormalities which in turn led to less of the more obvious obstetrical difficulties and disasters. For some years, however, the mildly contracted pelvis caused trouble especially in second and third births but now even mildly contracted pelves are becoming less common.

A further advance was made when the Local Government (Scotland) Act, 1929, gave local authorities power to build institutions and it is to the credit of the Scottish local authorities that many of them took advantage of this power and began to build maternity hospitals. Some took over houses temporarily and adapted them for this purpose. These hospitals required obstetricians and gradually expert care became available in most parts of the country. In 1926 there were between 250 and 300 beds for maternity purposes in the country—in 1934 the number was approximately 1,064. There were in 1948 approximately 2,900 maternity beds in the country and this number has increased to about 3,000 at the present time. This provision enables almost 70 per cent of the total births to take place in institutions where there is or should be expert care. While bed provision might be still more ample, it is now sufficient to admit all cases likely to exhibit abnormality and, if prenatal care were adequate, all such women ought to be admitted in time for elective and not emergency treatment. This fact is being generally appreciated for in the enquiry into prematurity conducted by the Department of Health for Scotland it was found that about 90 per cent of premature infants were delivered in institutions.

Until 1937 local authorities had little or no control over domiciliary midwifery except for women attended by midwives in their area, but

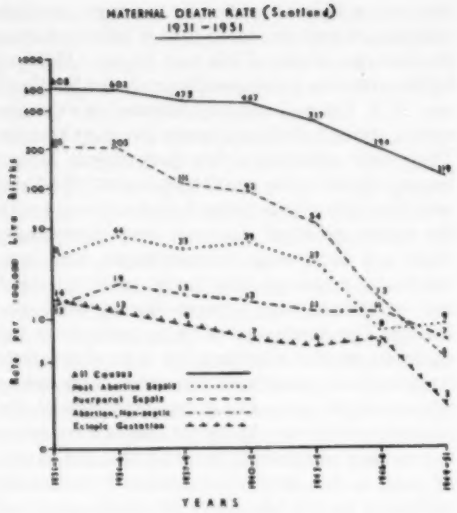
in that year the Maternity Services (Scotland) Act was put on the Statute Book. This Act compelled local authorities to make provision for the care of the woman in her own home throughout pregnancy, parturition and the lying-in period by providing a midwife, a general practitioner and also specialist obstetrical, and anaesthetist help, where necessary. The result was that every local authority which had not previously appointed either a consultant obstetrician or allowed a choice of consultant obstetricians then made arrangements for such a service. Because of the imminence of war and the necessity for concentrating on air raid precautions many of these services were not in full running order until 1941. The war, however, had another effect in that emergency maternity hospitals were opened up in different parts of the country to deal with evacuated pregnant women. These hospitals, too, required expert skill and obstetricians were placed in areas where their services were very badly required. These institutions, housed in private homes with little or no adaptation and the minimum of equipment, during their period of existence attended rather more than 7,800 cases. There were 4 maternal deaths—a rate of 0·53 per 1,000 live births—when the average Scottish rate was 3·7. The stillbirth rate was 18 per 1,000 live and stillbirths when the average Scottish rate was 36 and the death rate of infants during the first two weeks of life was 10 per 1,000 live births when the corresponding rate for Scotland was 27·5. The patients were selected to a certain extent, though abnormal cases did slip through. They were admitted a few days before labour began and it is quite possible that good food and rest from household duties had much to do with the results achieved. Labours were surprisingly short and easy, while haemorrhages, both prenatal and postnatal, practically never occurred and conditions like uterine inertia were unknown. The experience of these institutions has made me wonder whether a few days of complete freedom from household and other cares before labour might not make a big difference to the efficiency of labour. Maternal deaths were never at any time numerically large so that the saving of even a few lives could make a noticeable difference to the Maternity Mortality rate and the experience of these hospitals undoubtedly contributed to the downward trend.

Table I shows the Maternal Mortality rate divided into its various individual causes of death according to certification. These calculations were made by Dr. P. L. McKinlay and from them graphs have been prepared to show the trends of these individual causes of death.

TABLE I

Maternal Death Rates (per 100,000 Live Births) from Individual Causes: Scotland, 1931–51
Dr. P. L. McKinlay

	1931–33	1934–36	1937–39	1940–42	1943–45	1946–48	1949–51
Post-abortive sepsis	31	44	35	39	27	8	9
Abortion, non-septic	13	19	15	13	11	11	7
Ectopic gestation	14	12	9	7	6	7	2
Other accidents of pregnancy ..	6	4	3	7	3	3	2
Placenta praevia	34	22	22	12	12	7	3
Accidental haemorrhage	23	24	18	19	12	11	7
Other puerperal haemorrhage ..	35	46	41	43	36	30	7
Puerperal sepsis	215	205	111	92	54	13	5
Puerperal albuminuria, convulsions	85	83	76	72	53	30	16
Uncontrollable vomiting	32	21	21	18	3	1	1
Other toxaemias of pregnancy ..	23	18	15	25	11	9	8
Phlegmasia alba dolens, embolism	32	39	40	39	31	18	13
Other accidents of childbirth ..	52	56	63	55	54	43	30
Other and unspecified conditions ..	11	9	5	9	4	3	9
All causes	606	602	474	450	317	194	119



GRAPH 3

Because of the small numbers involved 3-year periods have been used in making the calculations.

Logarithmic graphs (Graphs 3, 4, 5 and 6) have been drawn for each individual cause of death and the total Maternal Mortality rate is inserted to give a clear picture of the individual causes depicted.

Graph 3

Puerperal Sepsis and Post-abortive Sepsis

The general trend for Puerperal Sepsis is down whereas the rate of Post-abortive Sepsis remained fairly level from 1931 to 1945 when it fell only to rise slightly in the last 3-year period.

Abortion, non-septic

The death rates from this cause rose slightly to 1934–36. Since then there has been a slight decline to the present time; but as therapeutic abortions come into this group of deaths perhaps more improvement could be looked for.

Ectopic Gestation

This rate has declined gently during the period of observation until 1946–48 when there was a slight rise, since when it has fallen to a very low level.

Graph 4

Other Accidents of Pregnancy fell from 1931–33 until 1937–39, then rose again with the early war period, and fell rapidly during the war. The gradient levelled out after the war and during the last year or so has fallen to a rate of 2 per 100,000 live births.

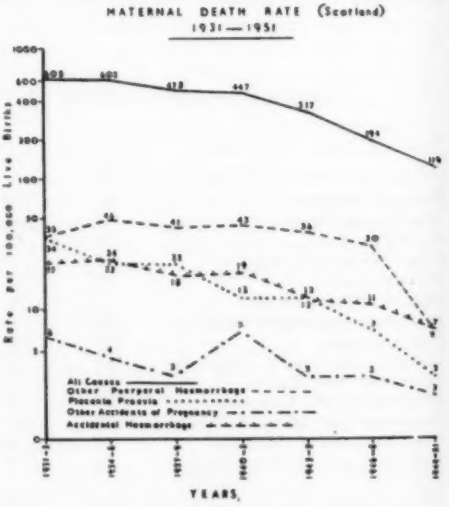
Placenta Praevia, once a formidable cause of death, during the period under review dropped gently until 1943–45 since when the fall has been more rapid.

Accidental Haemorrhage, formerly important as a cause of maternal death, remained fairly steady until 1940. Since then it declined gently until 1948, when a rapid decline has set in.

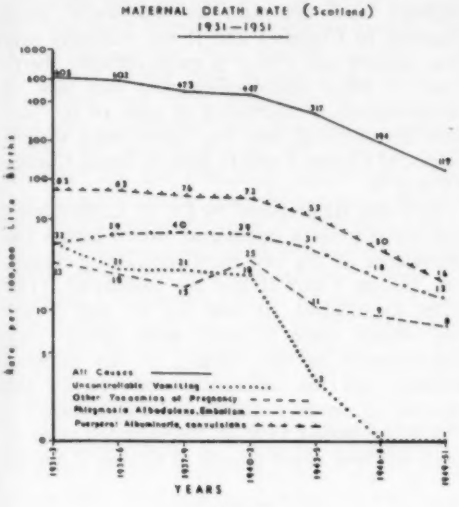
Other Puerperal Haemorrhage. This group of causes includes third stage primary and secondary post-partum haemorrhages and remained a considerable cause of death until 1946–48, since when a rapid fall has taken place.

Graph 5

Puerperal Albuminuria and Convulsions. Under this title are grouped Pre-eclampsia, Eclampsia,



GRAPH 4



GRAPH 5

etc. In former years these, the second highest group of causes of death, have declined gradually until 1940–42, then more rapidly during the latter war years and on until 1948, since when the rate has fallen to 16 per 100,000 live births. Improvement still could be looked for here.

Uncontrollable Vomiting remained fairly steady until 1940–42, since when it has fallen rapidly and as a cause of death is now virtually extinct. Uncontrollable vomiting has been considered as a toxaemia and also as a psychosomatic condition. The fall during the war was ascribed to the fact that women had many things other than themselves to think about. Had that been so, the rate might have been expected to rise after the war but this has not occurred. So the possibility is that perhaps this condition may have been initiated by a minor food deficiency which for some reason or other had disappeared. Also because of better clinical teaching given to medical students during the last decade or so medical practitioners appreciate the potential danger of the condition and send such cases to hospital much earlier.

Other Toxaemias of Pregnancy fell slightly until 1937–39, rose somewhat during the early war period but fell rapidly during the latter years of the war and since then the decline has been more gradual. Toxaemia, however, is still a significant contributory factor in the total rate.

Phlegmasia Alba Dolens and Embolism rose gradually from 1931–33 and remained at a fairly high level until 1940–42. Like Other Causes of Death it fell somewhat during the later years of the war and has continued to fall but the decline is gentle and it is even now the third highest individual cause of death.

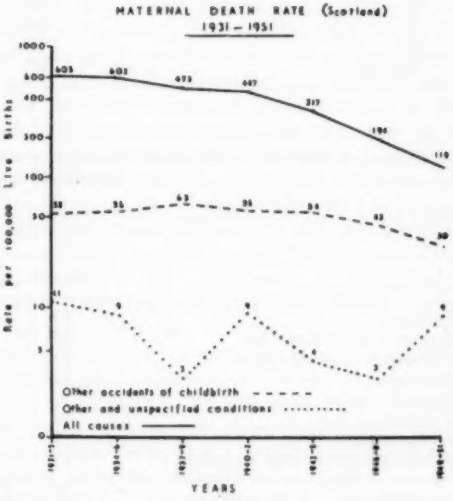
Graph 6

Other Accidents of Childbirth in 1931 were the third highest group of conditions which were a cause of death. These rose until 1937–39, since when they have fallen, but still remain the chief component of the Maternal Death rate.

Unspecified Conditions have fluctuated but on the whole have remained much the same throughout the period under review.

The Maternal Mortality rate still continues to fall and in 1953 there were 85 maternal deaths including 13 from abortions. This represents a Maternal Mortality rate of 0·9 per 1,000 births, live and still, or a rate of 0·77 excluding death from abortion.

Maternal Mortality varies with social class and Table II prepared by Dr. McKinlay



GRAPH 6

shows the class differences in mortality corrected for age of mother. Because the number of deaths in each year is small, the years 1939–40 have been grouped together and contrasted with the years 1944–50 inclusive.

In pre-war years, with the exception of the peak in Class III, Maternal Mortality increased with descent in the social scale. While all rates have fallen, this pattern has remained in the post-war period with the exception of the rate for the unmarried mother. Since the war local authorities have given more intensive care to this group of women. The vast majority are primigravidae and their pregnancies carry the risk peculiar to first births, yet as a class they have experienced a tremendous improvement. Might not freedom from financial and social obligations have had some influence on the result? The rate of decline in mortality has been greatest among unmarried mothers and decreases as the social scale ascends. In Classes I and II the mortality rate was already low and it is more difficult, therefore, to effect improvement but this lack of improvement is interesting in view of the fact that the stillbirth rate has fallen more steeply in Social Classes I and II than in Social Classes IV and V.

In Table III prepared by Dr. P. L. McKinlay are set out for a condensed list of causes the experience of the two most contrasting classes, i.e., classes I and II and the unmarried. (The rates for Classes III and for IV and V are not shown since in each cause group they approximate so very closely to the national average and the differences observed on the number of deaths available are insignificant.)

For the period 1939–40 the recorded rates of each of these cause groups in Classes I and II

TABLE II

Maternal Mortality per 100,000 Births, Adjusted for Age According to Social Class of Father
Dr. P. L. McKinlay

Social Class	1939–40	1944–50	Ratio of Rates for 1944–50 Expressed as a Percentage of 1939–40 Rate	Percentage Rate of Decline
I and II	273	161	59	41
III	459	214	47	53
IV and V	421	189	45	55
Illegitimate	618	192	31	69

TABLE III

Maternal Mortality by Cause Group in Classes I and II and Unmarried Mothers—Rates per 100,000 Births Standardized for Age of Mother
Dr. P. L. McKinlay

	1939–40			1944–50		
	I and II	Unmarried	Total	I and II	Unmarried	Total
Abortion	19	237	40	7	72	22
Ante-partum haemorrhage	28	12	39	13	8	19
Post-partum haemorrhage	24	60	43	15	16	21
Eclampsia	38	80	68	33	19	30
Other toxaemias	27	70	43	15	14	15
Accidents of birth	38	23	58	30	21	41
Puerperal sepsis	59	136	77	15	21	20
Puerperal embolism and thrombosis ..	27	36	40	25	8	20
All causes	273	618	426	161	192	199

are lower than the national rate, which suggests that the more favourable experience may be due to general rather than specific factors. The experience of the 1944–50 period in respect of eclampsia and other toxaemias of pregnancy and also of puerperal embolism and thrombosis shows no advantage over the national rates although for the remaining causes their rates are more favourable than the national rate; for unmarried women however the picture is different. In the earlier period the chief cause of their excess mortality was due almost entirely to abortion and puerperal sepsis whereas the latter period shows that their rates in all causes have improved and are on the whole better than the national average though they still show excess mortality from abortion.

The last 148 maternal death reports received by the Department of Health for Scotland have been examined. These deaths occurred in the years 1951, 1952 and the first half of 1953, but are not representative of all areas in Scotland.

In those examined 4 deaths had no connexion with pregnancy beyond that of time. The causes of death were carcinoma, subarachnoid haemorrhage, intestinal obstruction and anaesthesia.

In 25 cases the woman was suffering from some condition from which she would have died ultimately but presumably pregnancy hastened the advent of death. The causes of death were advanced tuberculosis, heart disease, thyrotoxicosis, essential hypertension, etc.

There were 77 deaths, i.e., 52 per cent, in which the death seemed unavoidable in the light of the present knowledge. In 60 per cent of these delivery was completed spontaneously.

In 13 instances death occurred because the woman did not seek or refused to accept antenatal advice. In a few others antenatal care was obviously not of the best but only in 1 could death be attributed entirely to faulty antenatal care.

There were 16 deaths from abortion all but 2 obviously procured and mostly by married women who had 4 or more children alive. In view of these findings there would seem to be need for a wider dissemination of the knowledge of contraception. These deaths are certainly avoidable and mental distress must be profound when women with young families whose present and future welfare depends on them deliberately incur such a risk.

In 2 instances post-partum care appeared to influence the fatal result. In 1 the patient herself was to blame.

There were 11 cases of bad midwifery, such as failed forceps before admission to hospital, high or mid-cavity forceps with resultant lacerations and extreme shock; forcible expression of the placenta within a few minutes of the end of the second stage of labour, ruptured uterus, etc. Such deaths from bad obstetrics may be few, but their prevention would still make a difference to the Maternal Death rate.

There were 21 deaths from eclampsia, pre-eclamptic toxaemia or albuminuria. In some instances every possible care appeared to have been taken, in others prenatal care was not of the best though in most of such instances the patient herself was as much to blame as her attendants. When such patients default from clinic or surgery a note to the Medical Officer of Health would ensure visitation as often as desired. All women showing high blood pressure or albuminuria could be visited weekly if information regarding them was passed to the local authority.

Twenty-five deaths were ascribed to embolism, mostly pulmonary embolism. In some, death was unavoidable and occurred during the course of a seemingly normal puerperium and therefore could not have been anticipated. In others there was the usual history of varicose veins. In 23 delivery had been spontaneous and easy; in 2 spontaneous after medical induction of labour. In none had there been anything indicative of any septic focus. In those where varicosity was mentioned, case histories do not say whether the varicose condition existed before pregnancy or whether it had arisen during the pregnancy. The majority of those women appear to be drawn from the Registrar General's classes III, IV and V, therefore presumably they would have had to take complete charge of their households during pregnancy. As indicated earlier in this paper it was women from these same three classes who were in the majority in the emergency maternity hospitals and there was no death from embolism. Should women suffering

in this way be admitted to hospital for a week or two before delivery?

In 22 cases Caesarean section was the operative procedure in effecting delivery. At times the operation was one of election, at other times one of emergency, but in all cases the history indicated that it was a necessary procedure.

The Stillbirth Rate

The Registration of Stillbirths (Scotland) Act was put on the Statute Book in 1938 and registration began in 1939. Since the beginning of registration the total stillbirth rate has fallen from 42 per 1,000 total births, live and still, to 26 per 1,000 births, live and still, in 1952, that is a fall of 37 per cent in a space of 13 years.

Table IV shows the stillbirth rates per 1,000 total births by age of the mother. The small

Table IV

Legitimate Stillbirths by Age of Mother per 1,000 Total Births

Year	All Ages	−20	20+	25+	30+	35+	40+
1939 ..	42	29	29	36	46	62	77
1940 ..	42	30	30	36	45	62	79
1941 ..	39	19	29	34	43	57	68
1942 ..	38	27	28	31	41	55	68
1943 ..	35	21	24	30	37	50	70
1944 ..	32	21	22	27	35	44	58
1945 ..	32	27	24	26	33	45	64
1946 ..	32	25	22	29	32	43	61
1947 ..	30	19	22	25	33	41	60
1948 ..	28	22	22	23	32	40	56
1949 ..	27	21	20	20	30	40	66
1950 ..	27	23	19	23	27	41	63
1951 ..	27	23	19	22	28	40	65
1952 ..	26	21	19	22	28	39	65
1953 ..	25	—	—	—	—	—	—

Table V

Stillbirths by Parity

Year	Number of Previous Children											Illegitimate Stillbirth Rate	Stillbirth Rate per 1,000 Births
	0	1	2	3	4	5	6	7	8	9	10+		
1939	49	30	32	41	43	43	53	59	58	61	86	48	42
1940	44	29	36	43	43	53	55	71	81	86	102	51	42
1941	44		30			49				60	63	50	40
1942	42	27	31	35	38	44	49	51	60	72	78	47	38
1943	37	23	30	36	42	53	49	59	78	54	97	42	36
1944	36	21	25	31	37	52	48	65	50	53	75	41	33
1945	35	23	29	33	37	40	56	48	77	79	74	37	33
1946	36	21	26	33	40	42	46	52	57	61	74	38	32
1947	33	21	26	31	38	39	42	53	48	47	76	42	30
1948	30	20	26	31	36	41	42	59	47	66	75	36	29
1949	28	17	24	31	32	43	54	64	42	61	80	35	27
1950	27	18	25	32	37	36	50	45	49	36	64	35	26·9
1951	27	18	23	30	36	41	60	56	41	67	78	37	26·6
1952	28	18	24	25	33	36	39	48	50	58	69	34	26·0

Table VI

Stillbirth Rates, Per cent of Average by Age of Mother and Previous Parity, Scotland 1946–50
Dr. P. L. McKinlay

Previous Parity	Age of Mother						
	−20	20−	25−	30−	35−	40+	All Ages
0	81	82	111	154	186	238	109
1	44	53	58	75	104	157	68
2	45	69	70	91	120	163	89
3	—	86	78	110	137	189	111
4–6	—	113	99	119	151	214	138
7+	—	—	114	127	189	255	197
Totals	76	74	84	108	142	207	100

numbers involved in the age groups under 20 and over 40, respectively, tend to make the rates fluctuate but the general trend of each age period since certification began has been downward and it is to be noted that the rates for women under 20 years of age are usually a little higher than those of the 20 to 24 age group. The 20–24 age period carries the lowest risk after which the risk of stillbirth appears to increase with advancing age.

Table V shows stillbirths by order of birth. From this Table also it will be seen that since registration began there has been a gradual reduction in the rates with each parity, the rate for primigravid women always being higher than for those bearing their second child, but while the rates for all parities have fallen the rate increases with advancing parity.

Table VI calculated by Dr. McKinlay shows the stillbirth rates per cent of the average by age of mother and previous parity in Scotland for 1946–50. Each factor of age and parity has its respective influence on the prospect of a stillbirth and there is a greater risk with increasing age and parity, except that among primiparae the foetal loss is heavier on the whole than for degrees of previous parity up to 4. Each factor is also of importance within the specific value of the other; thus, for individual parity groups, the rates increase with advancing age of the mother while in the differing age groups the heaviest rates are found among primiparae and the higher degrees of multiparity.

TABLE VII

Correcting Factors for Maternal Age and Parity and Stillbirth Rates in Different Social Classes, Scotland, 1949–50 Dr. P. L. McKinlay

Social Class	Stillbirth Rates Per Cent of Average Rate			
	Crude Rates	Corrected for Age	Corrected for Parity	Corrected for Age and Parity
I ..	62·4	59·8	67·1	60·3
II ..	87·9	81·7	91·9	82·5
III ..	96·1	97·7	97·5	97·8
IV ..	107·0	108·1	103·8	107·9
V ..	124·3	122·2	117·0	120·9
Totals	100·0	100·0	100·0	100·0

Table VII shows that when stillbirth rates are corrected for age and parity class distinction is of far greater moment than even age or parity in producing a high stillbirth rate and the rate in Class V is almost double that of Class I. The problem for the future therefore is to make the physical condition of women of Classes III, IV and V as good as that of Classes I and II but here again the problem is why there should be these differences and whether they are due to genetic differences or whether to the amount of physical work the woman has to do in caring for household and children. Once more the good results obtained in the emergency maternity hospitals raise the issue of the value of a period of enforced rest prior to labour.

Table VIII shows the stillbirth rates per 1,000 total births live and still, for individual causes of death and their respective effects on the fate of the foetus. From those figures it is clear that as far as General Diseases of the mother are concerned, these in themselves have never been a major cause of stillbirth, but also that there has been little change in the rates since registration began.

Maternal toxaemias and ante-partum haemorrhage always were responsible for a considerable proportion of intra-uterine deaths and in the years under review these have dropped by 36 per cent.

Developmental defects in the foetus incompatible with separate existence would appear to have been uninfluenced by any medical advance.

There has been a welcome fall of more than 50 per cent in foetal death due to difficult labour. In the earlier years of certification there was obviously some laxity in stating the cause of death and considerable numbers of stillbirths had to be classified in the Ill-defined and Unknown class, but with the increasing interest taken by the profession this matter has gradually righted itself and this group has dropped to less than a third of what it was formerly, whereas the group of Other Defined Causes has risen to almost twice what it was in 1939. During the last 3 years the Registrar General has further divided this latter group into Placental and Cord Conditions and Other Defined Causes. For a few years now these rates have remained pretty much the same. It would seem, therefore,

that special care must be given to women suffering from general diseases as well as to those suffering from toxaemias and antepartum haemorrhage. In the light of present knowledge it does not seem that much can be done about foetal defects. The rate due to difficult labour has been falling year by year and it is hoped may continue to improve. The same observation may be made on cord and placental conditions and other defined causes. Though ill-defined and unknown causes have dropped remarkably no stillbirth should be certified as of unknown cause until after all possible methods have been tried to elucidate the cause of foetal death.

A Table has been prepared showing the rate of foetal defects by age of mother and by parity and also birth injuries by age of mother and parity. Because of the small yearly numbers the years 1949, 1950 and 1951 have been grouped together in calculating the rates.

Tables IX and X show that at ages under 20

TABLE VIII

Scotland

Stillbirth Rate by Cause per 1,000 Total Births, Scotland 1939–52

Year	General Diseases of Mother	Toxaemias	Ante-Partum Haemorrhage	Foetal Defects	Difficult Labour	Other Defined Causes	Ill-defined or Unknown Causes	All Causes
1939 ..	0·8	3·7	5·5	5·9	9·5	2·9	13·4	42
1940 ..	0·9	4·4	5·0	6·1	8·9	3·1	13·7	42
1941 ..	1·3	4·0	5·1	9·0	11·3	0·7	8·1	40
1942 ..	1·2	4·2	5·2	6·8	10·4	4·2	6·3	38
1943 ..	1·2	3·4	4·3	6·1	9·3	4·5	6·9	36
1944 ..	1·0	2·8	3·9	5·9	9·1	4·4	5·5	32
1945 ..	1·0	3·0	3·7	6·7	8·5	4·4	5·5	33
1946 ..	1·1	2·7	3·7	6·0	8·9	4·0	5·9	32
1947 ..	1·1	2·7	3·5	5·2	8·6	4·8	4·6	31
1948 ..	0·9	2·1	3·9	5·5	7·3	4·4	4·7	29
1949 ..	0·8	2·4	3·8	5·1	6·3	4·7	4·0	27

Year	General Diseases of Mother	Toxaemias	Ante-Partum Haemorrhage	Foetal Defects	Difficult Labour	Other Placental and Cord Conditions	Other Defined Causes	Ill-defined or Unknown Causes	All Causes
1950 ..	0·8	2·3	3·9	4·8	5·4	4·1	0·9	4·7	27
1951 ..	0·8	2·7	3·8	5·1	4·8	3·9	1·1	4·2	27
1952 ..	0·8	2·1	3·8	5·6	3·9	4·8	1·1	3·9	27

TABLE IX

Congenital Malformation and Birth Injury by Age of Mother

Years 1949–51	−20	20+	25+	30+	35+	40+	All Ages
Congenital Malformation	5·18	4·57	4·15	5·30	5·83	10·35	5·02
Birth Injury	4·69	3·94	4·67	6·58	10·07	14·28	5·97

TABLE X

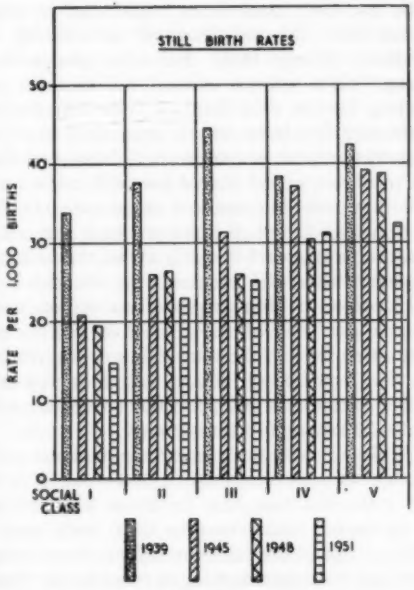
Congenital Malformation and Birth Injury by Parity

Years 1949–51	0	1	2	3	4	5	6	7	8	9	10	All Groups
Congenital Malformation ..	5·17	3·81	5·11	5·64	4·60	6·94	9·21	9·92	8·30	7·22	11·08	5·02
Birth Injury ..	6·71	3·79	5·09	6·04	7·97	9·58	12·44	11·69	10·51	11·73	12·31	5·97

and from 30 years onwards the risk of a stillbirth due to malformation tends to be above the average risk and that the risk of a stillbirth for primigravidae is higher than the risk with a second or third pregnancy—the risk being considerable from parities above the fifth.

In preparing the parity tables it was impossible to classify illegitimate stillbirths into parities so all illegitimate stillbirths have been placed in the O parity group and calculated against a denominator containing all legitimate first births, live and still, plus all illegitimate births live and still. Even with this "weighting" of the O parity group the rate is still less for the first than for the fifth and subsequent pregnancies, so it would seem that on the average if birth injury sufficient to cause stillbirth is to be kept as low as possible families should be limited to 4.

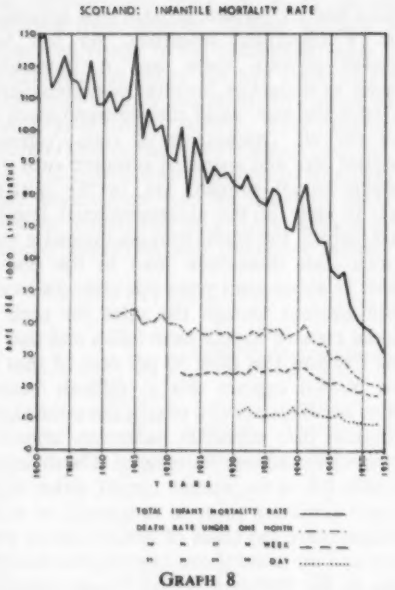
Graph 7 shows the stillbirth rates by social class for the years 1939, 1945, 1948 and 1951. Prior to the last war stillbirth rates were high in all social classes with a noticeable peak in social Class III (skilled artisan) and another in Class V (unskilled labourer). As has been indicated already there was a tremendous increase in maternity hospital provision during and after the war—food rations were much the same for all, irrespective of class; intensive antenatal care and specialist obstetric care were available to all women; yet, in the post-war years, in spite of the aforementioned levelling social factors, the stillbirth rates showed a more obvious class distinction than in the pre-war period. In subsequent years this class distinction is still obvious though the rates for each individual class of society have fallen and that for Class I is now less than 50 per cent of that for Class V. To explain this is difficult because women of all classes can obtain the same skilled obstetrical care especially when an abnormal pregnancy or delivery is expected. The difference probably lies in the woman herself, either in her physical condition prior to pregnancy or in the intelligent care she takes of herself during pregnancy and the table above showing the Stillbirth Rates in the Different Social Classes corrected for the factors of age and parity makes it clear that social class seems to be the important factor in determining the rate. Earlier in this paper when discussing Maternal Mortality I made a passing reference to the low stillbirth rates of the emergency Maternity Hospitals. The women admitted to those hospitals came from social Classes III, IV and V, and, though to some extent obstetrically selected, presumably had the mental and physical make-up of their class, yet the Stillbirth Rate was low. Did the few days relief from all domestic and other obligations, plus rest in hospital prior to labour have any effect in tending to produce a more viable foetus? There may be nothing in this but it is a point worthy of consideration.



GRAPH 7
Mortalities of Pregnancy by Social Class of Father.

THE INFANT MORTALITY RATE

The Infant Mortality Rate which comprises all deaths of children under a year per 1,000 live births should be divided into those infant deaths which are part of the child-bearing process and those which are part of the business of living. Graph 8 gives the Infant Mortality Rates for Scotland from 1900 to 1951, i.e., half a century.



GRAPH 8

From 1910 the Registrar General published data concerning the deaths and death rates under one month. Later, as realization of the causes of neonatal deaths became clearer data were given showing infant deaths at ages under one week and under one day of life.

Since 1900 the Infant Mortality Rate has fallen steadily though with fluctuations until 1940, since when it has fallen very steeply to the present rate of 31 per 1,000 live births in 1953.

The graph clearly shows that the tremendous improvement has been in the age period between 1 and 12 months. There was little improvement in the neonatal mortality rate until 1940 when a steep decline began. Here again, however, the improvement is chiefly in the older age period, i.e., between the ages of 1 week to 1 month; whereas the death rates under 1 day and between 1 day and 6 days show little improvement. At the present time more infants die under the age of 6 days than between 6 days and 1 year.

It is these first weeks of life which especially concern the obstetrician. During the year 1952, apart from 361 stillbirths due to birth injury, there were 258 infants who died from that cause and it is worth remembering that apart from those who die there are always some who live as mental defectives, dull and backward children, spastics, etc. In the country there are about 8,000 persons suffering from mental defects living in institutions or boarded out with guardians and about 5 per cent of these are defective through birth injury. As each one costs the state about £250 per year and may live for 65 or 70 years the cost to the nation is enormous as well as being unnecessary. Every endeavour should be made to reduce these cases to a minimum. In the same period asphyxia and atelectasis accounted for 412 infants, of whom 90 per cent died within the first 6 days of life. Whether or not such deaths can be avoided I leave to clinicians. In the light of present knowledge congenital malformations cannot be avoided.

Prematurity is the largest single cause of neonatal death and 80 per cent of premature infants die under 1 week of age. The Department of Health for Scotland, in collaboration with the local authorities, conducted a pilot survey into the incidence of prematurity in Scotland. Every local authority co-operated though some returns arrived too late for including in the data used. It was found that premature live born infants amounted to 5 per cent of the total of live born children but that the incidence varied from 4 per cent in the rural to 6·3 per cent in congested urban areas. Of the 4 principal cities, Edinburgh had the most favourable rate of 5·83 (still above the national average) while the incidence in Dundee was 8·12 per cent. Though premature infants were only 5 per cent of the total live births they accounted for half the total infant deaths during the first 3 months of life and their mortality rate in this period was 200 per 1,000 compared with under 20 among full-time infants.

Table XI indicates clearly the tenuous hold on life of the premature infant—not only in the first week but even for those who survive to between 1 and 3 months their death rate is 3 times that of the full term infant. Most intensive and intelligent nursing is required for these babies and special efforts should be directed to prevent the occurrence of retrolental fibroplasia.

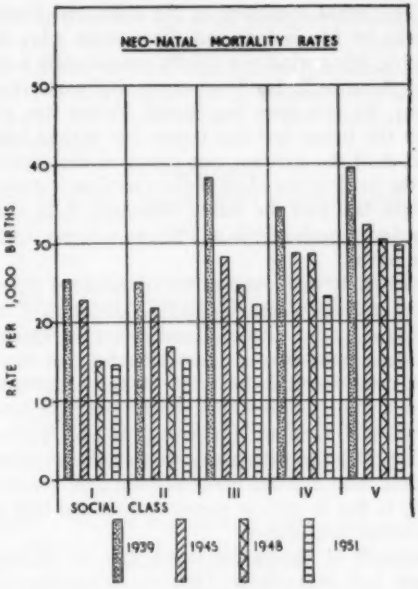
TABLE XI

Death Rates at Different Periods of Life in Premature and Full-time Infants, Scotland, 1952
Rates per 1,000 Live Births

	Total	Pre-mature	Full-term	Ratio of Rates in Pre-mature: Full-term Infants
Under 1 day ..	8·10	67·39	6·05	11·14
1–6 days ..	8·92	93·03	4·51	20·63
1–2 weeks ..	2·12	19·06	1·24	15·37
2–3 weeks ..	1·13	4·77	0·94	5·07
3–4 weeks ..	1·04	6·13	0·77	7·96
Under 1 month	22·31	180·38	13·51	14·09
1–3 months ..	6·08	15·43	5·60	2·76

The education and care of a blind child is even more costly than that of a mental defective while the tempo of the modern world must make their life very hard and difficult. The deaths of full-time infants might become almost negligible if birth injuries could be avoided. The Department of Health for Scotland intend to conduct a further survey during 1954 into prematurity; this time, however, an endeavour will be made to include premature stillbirths as well as premature live births. More research might shed light on some of the present obscurities regarding the causes of prematurity.

Graph 9 shows the neonatal loss grouped according to social class and as with the stillbirth rates there is a gradual increase in mortality as the social scale descends. Those differences in foetal and neonatal death rates between social classes would seem to be due to the greater number of nonviable foetuses born to the less socially privileged women and Dr. J. W. B. Douglas (1951) has published data to show that if infants or foetuses weighing less than 5½ pounds at birth were excluded there would be little difference in the rates between one social stratum and another. It is generally taken for granted that viability is related to the period of gestation but Gibson and McKeown's (1950) work seems to show that duration of gestation does not vary significantly with social class but that there is a significant difference in the birth



GRAPH 9

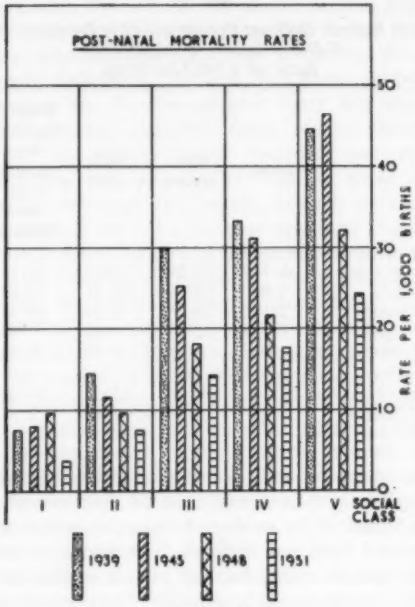
Mortalities of Early Infancy by Social Class of Father.

weights of infants born to women of the different social classes (1951). This would appear to be in agreement with Professor Baird's (1947, 1949) work on stature in relation to birth weight. What causes this difference is of importance to public health workers because if possible it should be prevented. Food may be a cause, but food in reasonable quantity and quality should now be available to all. Pre-natal care may at times be better in Class V than in Class III, but too often women who know how to get the best attention yet do not take the benefit of that care. This gives rise to the thought that such carelessness or seeming carelessness is a rejection of the pregnancy in the same way as is the procured abortion. Apart from the case of the unmarried mother, most of the procured abortions occur in the higher multiparae who feel that they are unable to cope with another child. It seems to me that women who show such seeming carelessness do not particularly wish to have another child and are therefore indifferent to its fate and their own welfare.

The infant mortality of the third and fourth weeks of life is low and the infants who die during this period are chiefly prematurely born and those suffering from congenital malformations. By this time the Health Visitor has got into the home and has begun her patient education of the mother, and much of the success of the work of the child welfare services is shown by the fact that the Infant Mortality Rate after the first month of life in 1953 was 11 per 1,000 live births.

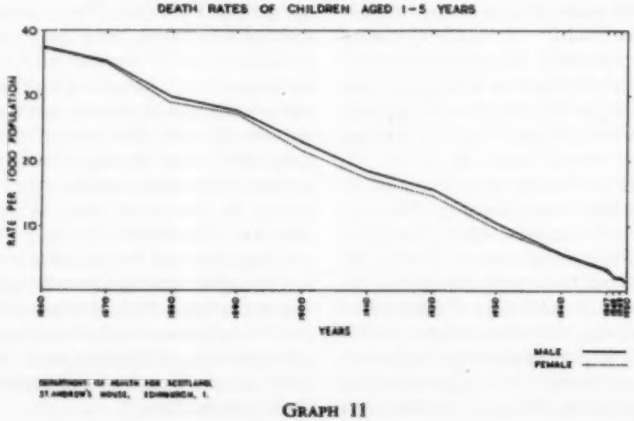
Graph 10 again shows the tremendous differences in the postnatal mortality of children of the different social classes. Intelligence in rearing children must play its part here for this death rate rises sharply with parity in the lower class families but does not change with parity in more privileged families (Gibson and McKeown, 1951). This rise with parity seems to be an urban rather than a rural manifestation and presumably is due in part to overcrowding and lack of maternal intelligence.

Graph 11 shows the death rate of children aged 1–5 years from 1860 on. This diagram must bring the realization that in so far as mortality was concerned, whatever may be said of the latter half of the nineteenth century, conditions became more favourable to early child life. The death rate began to fall in 1860 and has declined steadily and is now so low that as far as mortality is concerned class distinctions tend to be wiped out. The highest individual group of deaths in this age period is Accidents and Violence—followed closely by tuberculosis. Tuberculosis in pre-school children means a domestic source of infection as nowadays milk



GRAPH 10

Mortalities of Infancy by Social Class of Father.



GRAPH 11

is seldom incriminated and it is hoped that B.C.G. inoculation will shortly provide protection against domestic infection. In 1952 there were 539 deaths of 1–5 year old children and of these 118 were due to accidents.

Summary

To summarize therefore, as far as individual causes of maternal mortality are concerned, deaths resulting from bad obstetrical procedures should cease but also improvement should be looked for chiefly in toxaemias leading to albuminuria and convulsions and also in embolism. It is worth giving consideration to the fact that a period of antenatal rest from social and other worries might be of importance in securing better results.

As regards stillbirth and neonatal death, more care in the selection and execution of obstetrical procedures should avoid needless deaths from birth injury. Efforts must be made by local authorities to improve the general physical condition of the less financially and socially privileged women but also more intensive antenatal care is needed to observe and deal immediately with early deviations from the normal. At postnatal clinics more instruction in family planning is essential to prevent pregnancies occurring too rapidly.

The later neonatal period and the care of the child up to school age is the province of the local authority and the general practitioner. Theirs is the difficult task of continuous education and efforts to this end cannot be relaxed if the well-being of the future mothers of the race is to be safeguarded.

References

Baird, D. (1947): "Social factors in foetal mortality." *Lancet*, **2**, 531.

Baird, D. (1949): "Social factors in obstetrics." *Lancet*, **1**, 1079.

Campbell, J. (1930): *Interim report to the Ministry of Health on maternal mortality and morbidity*. H.M. Stationery Office, London.

Douglas, C. A. (1945): "Maternal and child health under war conditions." *Trans. R. sanit. Ass. Scotland.*

Douglas, C. A., and McKinlay, P. L. (1953): "The incidence of prematurity in Scotland and its importance in early infant mortality." *Scotland Dept. Health, Health Bull.*, **11**, No. 1.

Douglas, J. W. B. (1951): *Population Stud.*, **5**, 35.

Gibson, J. R., and McKeown, T. (1950): *Brit. J. soc. Med.*, **4**, 221.

Gibson, J. R., and McKeown, T. (1951): *Brit. J. soc. Med.*, **5**, 177.

Kinloch, J. P., Smith, J., and Stephen, J. A. (1928): "Maternal mortality in Aberdeen." *Ann. Rep. Scottish Bd. Health*. p. 149.

McKinlay, P. L. (1947): "Maternal mortality in Scotland." *Rep. Registrar General Scotland.*

McKinlay, P. L. (1952): *Social class variations of parity and age of mother and their influence on still birth rates in Scotland.*

McKinlay, P. L. (1954): "Social class differences of maternal mortality in Scotland." *Scotland Dept. Health, Health Bull.*, **12**, No. 2.

CHORIOCARCINOMA

A Report of Two Cases with Unusual Features

BY

JOHN PEEL, M.A., B.M., B.Ch., F.R.C.S., F.R.C.O.G.
Obstetrical Surgeon

JOHN DAWSON, *M.C.*, M.D., M.R.C.P.
Late Senior Medical Registrar

AND

GORDON MATHER, M.B., M.R.C.P.
Senior Medical Registrar
King's College Hospital

CHORIOCARCINOMA has attracted much attention since its first description by Saenger (1889). He named the growth deciduoma malignum, but Marchand (1898) was the first to recognize its origin from foetal villi. By 1903 Teacher was able to collect and analyze 188 cases from the literature. Recently the subject has been reviewed by Mathieu (1937), Brews (1939), and Acosta-Sison (1949). Park and Lees (1950) and Novak and Seah (1954) have made important contributions on the pathological aspects of the disease. It is a rare form of cancer and some idea of its frequency is given by Schumann and Voegelin (1937) who found that one in 13,000 pregnancies was followed by choriocarcinoma over a five-year period and Brews (1939) who found that one case was admitted to the London Hospital every two years. Two unusual cases are recorded here which illustrate several features of the disease which are of practical importance.

CASE REPORTS

Case 1. A parous woman aged 34 years came to hospital in April, 1950 complaining of cough with blood-stained sputum for four months. In August, 1949 she had attended another hospital because of slight vaginal bleeding for one week, after amenorrhoea for four months. The uterus was found to be slightly enlarged and the cervix closed; curetted fragments showed no evidence of chorionic villi on microscopic examination. Within a week she developed a dry cough with aching pain in the left shoulder, and also had further vaginal bleeding which persisted. During the next six weeks she lost her appetite and occasionally vomited. The cough steadily increased in severity through the winter and by December she was producing small amounts of blood-streaked mucus almost every day. She suffered from increasing fatigue and palpitations. A continuous discharge of altered blood led to another curettage in February, 1951; again no chorionic villi were found. After examination she had no further loss for two months and then had a normal five-day period. This was followed by a brown discharge for two weeks, ceasing a fortnight before admission.

Past History. In 1941 she had a stillbirth at seven months and in 1946 and 1948 normal births.

Physical Examination. The general condition was good. Respiratory system: early finger clubbing, trachea displaced to the right. On the left side above the third rib and the scapular spine an impaired percussion note, diminished vocal resonance and distant breath sounds with scattered crepitations were found. The abdomen, cardiovascular and nervous systems were normal. Vaginal examination: bulky mobile uterus, cervix one finger tip dilated and oozing blood.

Investigations. Chest X-ray (26th April, 1950): The left lung showed consolidation of the upper zone and patchy consolidation in the mid and lower zones. The right lung showed a lesion in the right mid zone. The *haemoglobin* was 64 per cent (9·4 g. per cent). *Sputum:* no chorionic cells were seen in four smears of blood clot. The *Aschheim-Zondek test* (9th May, 1950) in 1/100 dilution was positive. Quantitative 24-hours estimation of urinary chorionic gonadotrophins (rat prostate weight) on 24th May, 1950 was 70,000 i.u., on 31st May, 1950 216,000 i.u. and on 15th June, 1950 190,000 i.u.

Course. For the first week she had slight fever and persistent tachycardia (90–100). She had virtually no cough but expectorated a little deeply blood-stained sputum about three times a day. The urine contained large quantities of gonadotrophin, confirming the clinical diagnosis of choriocarcinoma.

Although there were secondary growths in the lung the entire uterus and both ovaries and tubes were removed. This was done in the hope that the metastases would regress following removal of the primary tumour. On 18th May, 1950 at operation there was no obvious primary growth and no secondary growths could be seen in the liver or elsewhere. A transfusion of two pints of blood raised her haemoglobin to 78 per cent (11·6 g. per cent). Her general condition remained good and she now produced no sputum. One week after operation radiotherapy was started. Treatment was given to two large fields, anterior and posterior, covering the whole thorax (180 Kv.; 8 M.a.; 0·5 mm. copper filter at 60 cm.). A surface dose of 925 r was given to each field in 14 sessions. Apart from some nausea and vomiting her condition remained unchanged, but the chest radiograph showed extension of the metastases. Treatment was stopped because she complained of continuous frontal headaches and blurred vision. During the next week she developed a left hemiplegia and papilloedema. Coma followed and she died 48 hours later, 32 days after operation and 8½ months after the onset of pulmonary symptoms which themselves had started at the end of the fourth month of her presumed pregnancy.

Pathology. (Prof. H. A. Magnus.) The curettings taken in August, 1949 and February, 1950 were re-examined, and fresh sections made from the original blocks. No evidence of choriocarcinoma was seen.

Operation specimen. The uterus was 9 cm. long. The ovaries and both tubes were attached. There were no lutein cysts. All appeared normal to the naked eye. Sections from three blocks of the body showed no trace of choriocarcinoma. The endometrium was atrophic. Sections of both ovaries were normal.

Necropsy. Lungs: the left upper lobe was completely replaced by a well circumscribed spherical mass of red and grey tumour tissue about 20 cm. in diameter. Throughout the left lower lobe and the right middle and lower lobes were numerous discrete red nodules of growth. The lymph nodes in the left hilum were much enlarged by haemorrhagic tumour tissue. Brain: the cut surface showed several large haemorrhagic metastases in the right cerebral hemisphere, involving the internal capsule and occipital lobe. There was a large deposit in the left occipital lobe. Metastases were also found in the liver, kidneys, spleen, mucosa of the ileum and parathyroid gland.

Histology. In the lungs there were typical deposits of choriocarcinoma, with an outer zone of polyhedral cells and eosinophilic syncytial masses with extensive central zones of haemorrhage and necrosis. The metastases in the other organs were similar. The operation scar in the pelvic floor showed no evidence of choriocarcinoma.

Comment. It is probable that the 4 months of amenorrhoea in the summer of 1949 were due to a pregnancy which ended in August, 1949. Choriocarcinoma must have been present at this time in view of the almost immediate onset of cough with pleuritic pain in the left lung, symptoms which later proved to be due to metastasis. The interval between onset and diagnosis was 8 months and the patient died 1 month later. Curettage at the time of the miscarriage and 6 months later produced no evidence of the primary growth and none was found despite a careful search after death. Neither hysterectomy nor radiotherapy had any effect on the course of the disease.

Case 2. A parous woman aged 31, with one child, sought advice in July, 1949 for recurrent vaginal bleeding of 4-months duration. There was no history of amenorrhoea or other evidence of pregnancy. The uterus was bulky but otherwise normal. On 2nd August a dilatation and curettage was carried out. The fragments were normal macroscopically but the histological report (Prof. H. A. Magnus) was as follows: "Sections show fragments of endometrium, some secretory and some non-secretory. A few areas contain normal looking decidual cells. No degenerate villi are seen. There are also several larger masses of chorionic tissue where the cells are pleomorphic with a fair number of multinucleate and hyperchromatic forms. These cells are infiltrating between muscle fibres and into the walls of blood vessels. The appearances are highly suggestive of chorionepithelioma." Expectant treatment was adopted as no urinary gonadotrophins were present and the patient was unwilling to lose the possibility of having more children. The test was repeated 1 and 3 weeks later and on each occasion was negative. Seven weeks after operation she had a normal 6-day period and 1 week later a small loss for one day.

At the end of November, 1949 she visited her doctor because of 2-months amenorrhoea and morning sickness. The uterus was found to be slightly enlarged but a pregnancy test was negative. On 11th December she bled from the vagina for 3 hours. After a week in bed the patient was again examined on 18th December. At this time she reported swelling of the breasts, palpitations and dyspepsia, symptoms which she had noticed during her first pregnancy. The uterus was enlarged and a normal pregnancy of 12-weeks duration was diagnosed in spite of a negative A.Z. test. These symptoms subsided and the urine again showed no gonadotrophins in two tests on 9th and 14th January. Two weeks later the uterus was found to be normal in size. It appeared, therefore, that the ovum had died and a carneous mole had formed. Dilatation and curettage was done on 2nd February. The histological report (Prof. H. A. Magnus) stated that the appearances were very similar to those seen in the section of August, 1949, with no alterations in the histological picture which would enable one to make a firm diagnosis of choriocarcinoma. The opinion of several other pathologists was sought; all agreed that there was no definite evidence of malignancy.

For the next 2 months she had a slight yellowish vaginal discharge. Amenorrhoea continued until May, 1950, when the patient consulted another gynaecologist

who diagnosed secondary amenorrhoea, and prescribed hormone therapy. For the next 5 months she received stilboestrol 0·5 mg. for 10 days followed by ethisterone 25 mg. b.d. for 4 days and then 8 days without treatment. Withdrawal bleeding only occurred once in September. In October she again complained of morning sickness and backache; she was examined and the uterus was found to be the size of a 12-weeks pregnancy. Three further A.Z. tests were all negative. Once again the uterus decreased in size. Curettage was not done but the patient was given stilboestrol in the hope that she would expel what was at first thought to be a carneous mole spontaneously. Slight pink discharge started early in 1951, but the patient was not seen again until March. Examination then revealed asymmetrical enlargement of the uterus and she was advised to enter hospital for laparotomy. Early in April she felt tired and ill and coughed up blood on several occasions. She then had a brisk vaginal haemorrhage and was admitted to hospital on 21st April.

Physical Examination. The general condition was good. Abdomen: a mobile tumour arising from the pelvis was palpable 2-fingers' breadth above the symphysis pubis. On vaginal examination the swelling seemed to be uterine in origin due to a tumour in the left cornu of the uterus. There were no abnormal signs elsewhere.

Investigations. Chest X-ray: The right lung showed 4 ill-defined areas of infiltration about 1·5 cm. across, 2 in the upper and 2 in the lower lobe. The left lung showed 3 similar shadows, 1 in the upper and 2 in the lower lobe. *Tomogram:* The shadows were sharply defined, circular in outline and of about equal size. *Sputum:* One smear and one section of blood clot showed no chorionic tissue. *Aschheim-Zondek tests* from 8th August, 1949 to 19th November, 1950 were negative on 9 occasions. They were positive on 21st April and 27th April, 1951.

Course. During the first few days she felt unwell with slight fever 99° F. (37·2° C.) and coughed up about 6 clots of blood each day. The absence of tubercle bacilli in the sputum, the discrete nature of the radiological shadows and the unusual gynaecological history suggested the possibility of choriocarcinoma which was confirmed when the urine was found to contain gonadotrophins. Five days after admission the uterus, ovaries and tubes were excised in the hope that the metastatic growths would regress following removal of the primary tumour. There was a spherical haemorrhagic mass in the anterior uterine wall, a secondary deposit in the right broad ligament and the left ovary contained a large luteal cyst. Two days after operation the right lower lobe collapsed but 24 hours later she coughed up 2 large blood clots and the lobe aerated again. She continued to produce about 3 clots of blood daily, but had no cough. Between the ninth and twenty-seventh day after operation she had 4 attacks of sensory epilepsy. In the worst attack which lasted for about 20 minutes she had aphasia, blurred vision and paraesthesia over the right side of the body, her mind was confused and there were some shock-like movements of the arms and legs. During the fit the reflexes were normal and afterwards there was no residual paresis or sensory impairment. The other episodes were milder but vision was always affected. They ceased entirely under the effect of phenobarbitone gr. 2-daily. On the eleventh day after operation ethinyl oestradiol 2 mg. daily was given by mouth, increasing to 4 mg. (100,000 I.U.) after 2 weeks. Oestradiol benzoate, 50,000 units daily, was given intramuscularly. After 22 days 4 tablets each of 50 mg. of oestradiol benzoate were implanted subcutaneously to give a daily release of 20,000 I.U. She gained weight and steadily improved. During the last 2 weeks her haemoptyses ceased except for one clot on 2 occasions. She was sent home to continue taking ethinyloestradiol. A review of the chest radiographs showed that none of the shadows had enlarged and those in the left lung and right lower lobe were smaller. She remained very well without cough or blood spitting for 3 weeks. The oestrogens had in no way upset her. She then noticed pain and bruising in the left thigh which spread down to the calf and up to the back. A week later the right buttock became numb and she felt pain in the right calf. The numbness then spread over both buttocks and the perineum. Ten days later she became incontinent of faeces and urine and found it difficult to walk. At this time she re-entered hospital. She had ceased taking the oestrogen preparations 5 days before because of nausea and vomiting. She had no haemoptysis or cough until she returned to hospital on 17th July. She was then found to have slight fever and cough with blood-stained sputum. There was loss of sensation to pain and light touch over the second to fourth sacral segments, absent ankle tendon reflexes, and generalized weakness but no wasting of the muscles of the lower limbs. The bladder was not distended. The chest X-ray showed that the shadow in the apex of the right upper lobe had not changed but a small new one had appeared above the right hilum. The shadows previously present in the right lower lobe and left lung could not now be seen. X-ray of the lumbar spine and sacrum was normal. The A.Z. test was still positive. The severe pain required continuous use of morphia. Because of retention of urine an indwelling catheter was inserted. After the first few days she had no further cough or sputum. On the sixth day radiotherapy was given to one field 20×7·5 cm. over the sacrum and lumbar spine (220 Kv. 15 M.A.; Thoraeus filter at 50 cm.). A total of 1,500 r was given in 6 doses spread over 9 days. Her pain was a little relieved but the signs were unchanged. Two weeks later she was still totally incontinent and had numerous bruises on the arms and legs. She then became rapidly worse, the liver enlarged and a tender rounded mass could be felt on its surface. Despite transfusions of blood and the implantation of 4×100 mg. of oestradiol benzoate she required increasing amounts of morphia and died in coma 4 months after operation.

Pathology. (Prof. H. A. Magnus.) Operation specimen: A uterus 10 cm. in length whose anterior wall contained a spherical tumour 5·5 cm. in diameter. It was soft and haemorrhagic, but had not penetrated to the abdominal surface. An ovoid metastasis 1 cm. in diameter lay in the right broad ligament; its cut surface was pink with a few areas of haemorrhage. The left ovary contained a single luteal cyst 1·5 cm. in diameter. Sections showed that the

uterine growth was composed of a central area of haemorrhage and necrosis and a peripheral zone of polyhedral cells arranged in sheets and separated by thin-walled blood vessels and blood-spaces. Numerous mitoses and occasional multinucleate syncytial cells were seen. The surrounding muscle was obviously invaded. The tumour in the broad ligament was of similar structure.

Comment. In this case the diagnosis of choriocarcinoma was first suspected from curettings obtained following irregular vaginal bleeding. The uterus was not removed at this time because of the persistent absence of urinary gonadotrophins. For the next 15 months the Aschheim-Zondek test continued to be negative despite periods of amenorrhoea. It only became positive when next tested 20 months after the first one, at a time when metastases had already occurred. Oestrogens given in very large doses after hysterectomy did not affect the course of the illness. The interval between onset and diagnosis was 24 months and death occurred 4 months later.

Discussion

The early diagnosis of choriocarcinoma depends upon a characteristic history, typical histological changes in curettings and a positive gonadotrophin test. However, each of these three criteria may be misleading, and the diagnosis thereby made difficult. The clinical course of events in the two cases here recorded was unusual. Cough and haemoptysis were prominent features and in one the presenting symptom; in both they were at first thought to be due to pulmonary tuberculosis. The radiological appearances were consistent with that diagnosis. Case 1 showed a single large shadow in the left upper lobe and ill-defined shadows on the other side, while in Case 2 there were scattered fluffy shadows in both lungs. It was only when the history of miscarriage and bleeding came to light that the pulmonary changes were correctly interpreted. This mode of presentation of choriocarcinoma, though rare, is well recognized and was noted by Teacher in 1903.

The chief hazard in diagnosis lies in the difficulty of interpreting the appearances of chorionic tissue removed by curettage. The microscopic diagnosis is difficult enough even when material from operation or post-mortem is available. Novak and Seah (1954) had 159 such specimens submitted to them as examples of choriocarcinoma but accepted only 74. The conditions which were usually confused with choriocarcinoma were benign hydatidiform mole, syncytial endometritis and chorioadenoma destruens. Both Meyer (1927) and Novak and Seah (1954) emphasize that the chief feature of malignancy which separates choriocarcinoma from these other conditions is the patternless overgrowth of masses of syncytial and Langhans' cells. Well formed villi are hardly ever seen, they were observed in only one of their 74 cases; associated changes are muscle necrosis, haemorrhage and leucocytic infiltration. Other signs of malignancy are, in this context, frequently deceptive and have led to the diagnosis of choriocarcinoma being made too often. Thus both hydatidiform molar tissue and normal trophoblast invade blood vessels; and also signs of active cell division can be seen in the trophoblast of young embryos while they are not infrequently absent in choriocarcinoma. The limited material furnished by curettage may not be representative and intensifies these difficulties; in Novak and Seah's material only 13 of 74 cases were diagnosed by this means before operation.

In our second case the persistent absence of gonadotrophins, the possibility that the small curetting was an atypical fragment of benign chorionic tissue and the patient's unwillingness to submit to operation combined to justify a policy of waiting. Six months later, after the second curettage, a number of pathologists saw the sections and none could make a firm diagnosis of choriocarcinoma and again the negative A.Z. tests were reassuring. However, in the light of the subsequent course of events and after re-examination of the curettings we conclude that choriocarcinoma was present from March, 1949 when vaginal bleeding started. Presumably the growth was confined to the uterus until some time in 1951 when metastases began to cause symptoms. This long latent period before diagnosis is most unusual, the average being about 6 months (Park and Lees, 1950). The difficulty in accepting longer intervals is that an intervening pregnancy usually cannot be excluded as it can in this instance.

It is in circumstances such as these when there is doubt about the pathological evidence, that gonadotrophin tests are thought to be most useful and decisive. As Zondek wrote in 1937 "In case histologic examination of the curettage

material is doubtful, which may sometimes be the case, assay of the urine for gonadotrophin factor is of greater significance in the diagnosis than the histologic examination", and Mathieu (1937) goes so far as to say "as long as there is living chorionic tissue present the A.Z. test will be positive". The course of events in the second case shows that the absence of gonadotrophin in the urine, even when prolonged, is not always a certain guide. We consider these tests to have been reliable since they were done in two different laboratories by experienced workers. A possible explanation of the absence of gonadotrophin is that their production was reduced by the oestrogens which were being given, but the dose was very small and this, therefore, seems improbable. There are some 13 cases in the literature where pregnancy tests have been negative while choriocarcinoma has been developing and 2 others where the A.Z. was only weakly positive. Analysis of these cases suggests at least three possible explanations: Firstly, the carcinoma may be too small to produce hormone at the time of testing, as in Schumann and Voegelin's case (1937) where the A.Z. test was negative for 2 months after the end of pregnancy, but not tested again for 6 months, when the diagnosis was obvious. Further examples are recorded by Cosgrove (1938), Rust (1938) and Trafford (1953). A second possibility is that the growth may be surrounded or damaged by haemorrhage which prevents the elaboration and absorption of gonadotrophin (Durburg, 1946). This would explain the occasional negative tests following a positive one as in the case of Tuchschmid (1943), and is comparable to the transient disappearance of gonadotrophin which may occur during a threatened abortion. Thirdly, in those cases where widespread growth has been found accompanied by negative or weakly positive tests (Sutherland, 1951) it is probable that the tumour cells produce less hormone. It is not possible, however, to correlate this with the cytology; according to Jones, Gey and Gey (1943) the Langhans' cells are the source of gonadotrophin, but in Sutherland's case the A.Z. was negative despite the predominance of Langhans' cells. Other cases with negative gonadotrophin tests for varying periods following the end of pregnancy have been recorded by Hajek and Bareuther (1936), 7 months; Wilson (1939), 17 months; Rubin (1941), one week; Dockerty and Craig (1942), 4 years (diagnosis doubtful); Tuchschmid (1943), 9 weeks; Schugt (1947), 3 months; Brews (1950), 9 months; Richli (1950), 13 weeks.

It seems likely in our Case 2 that the small growth, recurrent haemorrhage and partial evacuation prevented the absorption of detectable amounts of gonadotrophin. A similar example is reported by Richli (1950) where recurrent bleeding occurred from a uterus which fluctuated in size, the A.Z. tests being also persistently negative. Whilst all these cases are unusual they serve to illustrate the fallibility of pregnancy tests in this disease. When miscarriage or pregnancy is followed by persistent uterine enlargement and bleeding, and the curettings are doubtful, a negative A.Z. test should not prevent the diagnosis of choriocarcinoma. On the other hand a positive test is not conclusive evidence of malignancy. In these circumstances successive quantitative estimations are much more helpful than qualitative tests (Hamburger, 1943). Gonadotrophin may be detected after a molar pregnancy for as long as 6 months and commonly up to 3 months. Hamburger's analysis of gonadotrophin tests in 72 cases shows that an increasing titre or one that is much raised (300,000 I.U.) after 1 month is very suspicious of choriocarcinoma if the mole has been completely removed. On the other hand the absence of gonadotrophins should not outweigh good histological evidence of malignancy. The limitations imposed by the small amount of material available may be overcome by repeated curettage.

The absence of a primary growth in the first case despite a very careful gross and microscopic examination of the excised uterus is difficult to explain. Resnick (1945) was able to collect 15 examples of choriocarcinoma with no uterine primary source. No satisfactory explanation for these cases has been given; in some instances the primary growth may have aborted or have been removed by curettage. In others, as in that of Novak and Koff (1930), the primary is thought to have regressed spontaneously just as metastases have been observed to do. This is

the probable explanation in our case as neither curettings nor the excised uterus showed any suspicion of choriocarcinoma.

The standard treatment for choriocarcinoma is removal of the uterus, ovaries and Fallopian tubes followed by radiotherapy, but these measures had no effect on the course of the illness in these two cases. Because oestrogens have been thought to retard the growth of normal chorionic tissue, these hormones were given in massive doses without affecting the outcome in the second case. The regression of some of the lung shadows may have been due to absorption of surrounding haemorrhage. Similar changes in the pulmonary metastases following oestrogen therapy have been reported by Kullander (1948) but the patient died nevertheless in 5 months. Another case was similarly treated by Hohlweg, Hahn and Braun (1952); she died from sepsis in 3 months but they interpreted the histological changes as showing recession and healing of secondary deposits though such features are seen in untreated cases (Novak, 1952). Hinglais and Hinglais (1953) have claimed a cure following treatment with oestrogens but the diagnosis was only based on a rising urinary gonadotrophin titre following a molar abortion; there was no histological proof. The effectiveness of any treatment is difficult to assess in this disease where the diagnosis in cases which recover is often open to doubt. However, in addition to the standard treatment further trial of massive doses of oestrogens (200–500 mg. daily of Stilboestrol or its equivalent) seems justified.

In the individual case, the discovery of local metastases is no contra-indication to hysterectomy, as there are several recorded instances of spontaneous regression of vaginal deposits (Hofmann, 1933; Brews, 1939). The evidence for similar behaviour of remote metastases is less solid. Of the 13 reported cases 5 are not acceptable because the evidence was based on clinical symptoms alone, which could have been due to pulmonary infarction or pneumonia (Phillips, 1911; Black, 1933). Another example resembled our Case 2 in that there was temporary shrinkage of the lung shadows, yet the patient later died from cerebral deposits, and autopsy revealed growths persisting in the lungs (Peightal, 1934). Other reported instances have had inadequate follow-up (Mazer and Edeiken, 1933) or have been based on inadequate evidence (Schmitz and Hueper, 1930). The only 2 examples with satisfactory evidence of spontaneous resolution are those of Lackner and Leventhal (1932) and Johnson (1951) with a follow-up of 5 years and 15 months respectively. An unusual case is reported by Maier and Taylor (1947) of the successful removal by lobectomy of a single pulmonary metastasis, the patient being well 3 years later. One can only conclude from the rarity of these examples that the appearance of remote metastases almost always precedes a fatal outcome, irrespective of the treatment given.

Summary

Two unusual cases of choriocarcinoma are described. Both had prominent pulmonary symptoms. In one no primary growth could be found at necropsy. In the other the A.Z. test was persistently negative and the interval between abortion and the development of metastases unusually long; the conclusion is that the presence of gonadotrophins is not essential for diagnosis of choriocarcinoma if there is good clinical and histological evidence. Treatment, including massive doses of oestrogens in one case, had no effect on the course of the disease.

Acknowledgments

We are grateful for the advice of Dr. Clifford Hoyle under whose care both patients came and to Professor H. A. Magnus for his help on the pathological aspects. We are indebted to Miss Mary Wood for the quantitative gonadotrophin tests.

References

Acosta-Sison, H. (1949): *Amer. J. Obstet. Gynec.*, **58**, 125.
Black, W. T. (1933): *Amer. J. Surg.*, **20**, 638.
Brews, A. (1939): *J. Obstet. Gynaec. Brit. Emp.*, **46**, 813.
Brews, A. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 317.
Cosgrove, S. A. (1938): *Amer. J. Obstet. Gynec.*, **35**, 581.
Dockerty, M. B., and Craig, W. M. (1942): *Amer. J. Obstet. Gynec.*, **44**, 497.
Durburg, J. R. (1946): *Amer. J. Obstet. Gynec.*, **52**, 484.
Hajek, O., and Bareuther, A. (1936): *Zbl. Gynäk.*, **60**, 322.

Hamburger, C. (1943): *Acta obstet. gynec. scand.*, **24**, 45, 79.
Hinglais, H., and Hinglais, M. (1953): *C.R. Soc. Biol., Paris*, **147**, 555.
Hofmann, H. (1933): *Mschr. Geburtsh. Gynäk.*, **93**, 311.
Hohlweg, W., Hahn, H., and Braun, G. (1952): *Arch. Gynäk.*, **181**, 139.
Johnson, W. R. (1951): *Amer. J. Obstet. Gynec.*, **61**, 701.
Jones, G. E. S., Gey, G. O., and Gey, M. K. (1943): *Bull. Johns Hopk. Hosp.*, **72**, 26.
Kullander, S. (1948): *Lancet*, **1**, 944.
Lackner, J. E., and Leventhal, M. L. (1932): *J. Amer. med. Ass.*, **98**, 1136.
Maier, H. C., and Taylor, H. C. (1947): *Amer. J. Obstet. Gynec.*, **53**, 674.
Mazer, C., and Edeiken, L. (1933): *Amer. J. Obstet. Gynec.*, **26**, 195.
Marchand, F. (1898): *Z. Geburtsh. Gynäk.*, **39**, 173.
Mathieu, A. (1937): *Surg. Gynec. Obstet.*, **64**, 1021.
Meyer, R. (1927): *Z. Geburtsh. Gynäk.*, **92**, 259.
Novak, E. (1952): *Gynecologic and obstetric pathology*. 3rd ed. Saunders, Philadelphia.
Novak, E., and Koff, A. K. (1930): *Amer. J. Obstet. Gynec.*, **20**, 153.
Novak, E., and Seah, C. S. (1954): *Amer. J. Obstet. Gynec.*, **67**, 933.
Park, W. W., and Lees, J. C. (1950): *Arch. Path.*, **49**, 73, 205.
Peightal, T. C. (1934): *Amer. J. Obstet. Gynec.*, **28**, 435.
Phillips, M. H. (1911): *J. Obstet. Gynaec. Brit. Emp.*, **20**, 299.
Resnick, L. (1945): *J. Obstet. Gynaec. Brit. Emp.*, **52**, 180.
Richli, R. (1950): *Gynéc. Obstét.*, **49**, 299.
Rubin, I. C. (1941): *Amer. J. Obstet. Gynec.*, **41**, 1063.
Rust, W. (1938): *Arch. Gynäk.*, **167**, 531.
Saenger, M. (1889): *Zbl. Gynäk.*, **13**, 132.
Schmitz, H., and Hueper, W. (1930): *J. Amer. med. Ass.*, **95**, 1413.
Schugt, P. (1947): *Zbl. Gynäk.*, **69**, 361.
Schumann, E. A., and Voegelin, A. W. (1937): *Amer. J. Obstet. Gynec.*, **33**, 473.
Sutherland, A. M. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 29.
Teacher, J. H. (1903): *J. Obstet. Gynaec. Brit. Emp.*, **4**, 1, 145.
Trafford, P. A. (1953): *Brit. med. J.*, **1**, 199.
Tuchschmid, G. (1943): *Schweiz. med. Wschr.*, **73**, 1493.
Wilson, K. M. (1939): *Amer. J. Obstet. Gynec.*, **38**, 824.
Zondek, B. (1937): *J. Amer. med. Ass.*, **108**, 607.

HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA*

Including Case Report

BY

P. COWELL BARKLA, *V.R.D.*, M.B., F.R.C.S.E., M.R.C.O.G.

Obstetrician and Gynaecologist

Nottingham Hospital for Women

IN any important pathological discovery, three distinct phases are noticeable. First there is the flash of illumination which makes manifest the origin or cause of the disease. In the second phase, the world literature contains reports of cases, the great majority of which substantiate the new appreciation of the disease. But with these reports come others which cannot be entirely reconciled with the new views on the origin or cause of the disease. The third phase is reached after years of patient collection of cases, when a modified form of the original theory is evolved which incorporates an explanation of the anomalous cases, as well as the standard ones.

The history of the discovery of the origin of hydatidiform mole and chorionepithelioma follows such a pattern. Until the discovery by Marchand in 1895, that these conditions originated from trophoblastic tissue, such cases presented a problem to the medical profession which it could do nothing to solve. Once the true nature of the condition was appreciated, a logical explanation of the behaviour of the disease was discernible, and from a survey of cases previously reported, and others which occurred subsequently, a standard pattern of the two conditions came to be recognized and accepted. But from time to time, cases were reported which did not conform to the standard pattern. The following case record is submitted as an example of such, as it shows an unusual sequence of events.

* Communicated to Meeting of North of England Obstetrical and Gynaecological Society, 19th November, 1954.

CASE REPORT

Mrs. E.M. was first seen by me on 30th January, 1938, being then aged 25 years. She complained of lower abdominal pain and irregular vaginal bleeding and lassitude, and on examination showed an abdomino-pelvic mass which extended almost to the level of the umbilicus.

Her previous history was long and complicated, and was not, in fact, fully elucidated until after the patient's death, which occurred on 31st January, 1938. For clarity, however, the case record is now presented consecutively.

In 1934, at the age of 21 years, being then unmarried, she was subjected to curettage of the uterus on account of abnormal uterine haemorrhage of which details are lacking. A hydatidiform mole was removed at that time; histological details are not available, but the report is quite unequivocal.

On 10th July, 1936, she was delivered by natural forces of a living child weighing 6 pounds 6 ounces after a 23-hours labour which occurred 3 days before the expected date of delivery. Vigilant antenatal care had detected no abnormality whatever, the labour was quite uncomplicated, and the puerperium uneventful.

Amenorrhoea persisted for 6 months after delivery. She then began to bleed vaginally, and the bleeding became almost continuous. Although apparently intelligent, she sought no advice until the bleeding had persisted for 5 months, i.e., until July, 1937. It was at this time that the possibility of a chorionepithelioma was first mooted, as the uterus was enlarged to the size of a 2-months pregnancy.

Unfortunately the patient then passed temporarily to the control of another institution, where she was admitted on 27th August, 1937, with a diagnosis of abortion complicated by pelvic peritonitis, the latter diagnosis being invoked to explain extreme pelvic tenderness. This condition subsided so far as the pain was concerned, but a palpable swelling was noticed on the left side of the pelvis, and an eventual diagnosis of chronic pelvic cellulitis had been made when she eventually discharged herself from this hospital on 27th November, 1937.

She was admitted to my care on 30th January, 1938. At this time she looked thin and tired, but she was apyrexial, although the pulse was 110 per minute. The abdomen contained a firm mass which extended across

the whole of the lower abdomen to about the height of one hand's breadth above the symphysis. This tumour was very tender on palpation, and appeared to incorporate the uterus and appendages, none of which could be felt apart from the tumour. The history of her condition has already been described, and all that need be added is that menstruation had been so irregular for the past year that no history could be obtained of the dates of the periods.

It was decided to perform a laparotomy the day after admission. Before opening the abdomen, a further vaginal examination was carried out under an anaesthetic, but apart from establishing the fact that the mass was well fixed in the pelvis, and immobile, no new information was obtained from this procedure. On opening the abdomen, the tumour was seen to be arising from the uterus, which was enlarged to about the size of a 5-months pregnancy. There were marked adhesions in the left side of the pelvis, where some small bowel was adherent. An incision was made into the uterus, in order to ascertain the nature of this swelling, when it became immediately apparent that this was a chorionepithelioma. Unfortunately, attempts to lift the tumour out of the pelvis had resulted in considerable haemorrhage from the left side of the pelvis, and the attempt to remove the tumour had to be abandoned. Despite all attempts at resuscitation, the patient died shortly after the closure of the abdomen.

A post-mortem examination revealed a large chorionepithelioma of the uterus most extensive on the anterior wall, but invading also the sides and back of the uterus, where it had spread locally to the parietal peritoneum, the pelvic cellular tissue and the left ovary. Two secondary metastatic deposits were found in the right lung, and a third in the left. Otherwise no secondary spread had apparently occurred. The sequence of events here would appear to have been: in 1934 a hydatidiform mole, in 1936 a full-time normal pregnancy, in 1938 death from advanced chorionepithelioma of the uterus.

Discussion

It will be appreciated that the condition of chorionepithelioma is of such rarity, that few individual gynaecologists have the opportunity to investigate more than a very few cases in the course of their career. In order that true evaluation of the condition may be made, it is necessary to study the literature. In so doing, one has been struck most forcibly with the relatively large number of abnormal types of case: cases, that is, which do not follow the standard pattern of the disease.

The anomalies which have been reported may be grouped as follows:

1. The occurrence of a condition, exactly similar in morphology, mode of spread and behaviour of tissue, in the male testis and mediastinum (Schlimovitz and Van Brown, 1950).

2. The occurrence of ovarian chorionepithelioma in virgins and in pre-pubertal children (Simard, 1937; Pick, 1904; Freund, 1929). Simard's case occurred in a virgin aged 17 years, whilst Pick and Freund reported chorionepithelioma in girls of 9 and 7 years of age respectively. Oliver and Horne (1948) found in a survey of the literature 9 cases of primary ovarian chorionepithelioma, including a case of their own, in pre-pubertal children.

3. The variable time lag between the onset of the established chorionepithelioma and any preceding abortion or pregnancy or hydatidiform mole. The usual gap is a matter of a few months only, but cases have been reported where hydatidiform changes have occurred in association with normal pregnancy, or where they have accompanied chorionepithelioma. MacRae (1951) reports a case of associated pregnancy and chorionepithelioma. At the other end of the scale, latent periods of up to 20 years have been recorded.

4. The divergence between the relative incidence of the development of chorionepithelioma of the uterus, tube and ovary, as compared to the number of primary pregnancies occurring in these sites. While figures of any accuracy are impossible to obtain, available data suggest that 1 case of uterine chorionepithelioma occurs for every 15,000 intra-uterine pregnancies. From a variety of sources (Schumann and Voegelin, 1937; Novak, 1947; Mathieu, 1939; Thomas, 1934; Walsh, 1935) it is computed that about 1 case of tubal chorionepithelioma occurs for every 1,500 tubal pregnancies. Madden (1950) has drawn attention to this discrepancy.

With regard to chorionepithelioma of the ovary, occurring as a primary condition, the literature contains reports of some 20 cases, all of which appear to be in association with a teratoma of the ovary (Oliver and Horne, 1948; de Zalka, 1928). In view of the total number of primary ovarian pregnancies reported, which is some 100–150, it is not surprising that no case of chorionepitheliomatous condition developing from a primary ovarian pregnancy has been recorded, if the incidence figures quoted above are borne in mind.

5. The occurrence in the female of extragenital chorionepithelioma with the apparent absence of a genital primary source. An explanation has been offered for these cases, the supposition being that the primary tumour has been cast off from the uterine cavity after the secondary spread has taken place. Freeth and McCall (1950) found 21 such cases in the literature, and added one of their own.

It is felt that insufficient attention has in the past been paid to the anomalous cases, and that the reports of such have tended to be neglected so far as correlating them with the "standard" case is concerned. It is true that some explanation has been offered to account for such cases: most commonly held is the belief that they occur as abnormal development of chorionic tissue in a teratoma, while the question of parthenogenesis has also been raised. They have tended to be placed in a category apart, despite the clinical similarity between them and other cases of chorionepithelioma. As it appears to be an unsound principle to postulate more than one cause for a single condition, it was decided to examine the abnormal cases to determine whether any common factor or connecting link could be found which might unite the common case with the anomalous one.

That the tissue involved is, as Marchand showed, the trophoblast, cannot be disputed. It was perhaps inevitable that this discovery coupled the condition of chorionepithelioma and vesicular change with a concomitant or preceding pregnancy, and this became one of the basic facts which gynaecologists have accepted ever since: and every case reported has been related as far as possible to such a pregnancy, either full-time or an abortion. Yet the condition of chorionepithelioma can occur, and run a course which is rapidly fatal, in circumstances where all possibility of pregnancy is excluded. The corollary may be asked in the form of the question—how far is it necessary to introduce a concomitant or preceding pregnancy to explain the occurrence of any individual chorionepithelioma?

It would appear that the normal trophoblast is developed entirely from cells of the fertilized ovum (Park and Lees, 1950). Is it impossible that, given the correct impetus, abnormal trophoblastic tissue may be formed on occasion from the unfertilized ovum, or even from the undifferentiated sex cell?

If this is possible, then, it is submitted, the anomalies noted previously can be explained.

1. The development of male testicular and even mediastinal chorionepithelioma follows the growth of trophoblast from the undifferentiated sex cell.

2. The explanation obtains for the occurrence of the disease in virgins and pre-pubertal girls, while the authentic lack of reports of cases occurring after the menopause is not surprising if it is postulated that the growth stimulus has vanished, or the ova have atrophied, or both.

3. The time relation to a preceding pregnancy becomes of no account if it is supposed that the vesicular or chorionepitheliomatous condition can develop from another ovum.

4. If the condition of chorionepithelioma does not require that the ovum be fertilized, then the difficulty of explaining the gross discrepancy between the ratio of cases of uterine chorionepithelioma to total uterine pregnancies and tubal chorionepithelioma to tubal pregnancies is overcome: there is, in fact, no relationship to be explained.

5. The question of apparently purely extragenital chorionepithelioma may be explained in the manner already noted; if so, there is nothing in the explanation to invalidate the postulate mentioned.

With regard to the so-called standard case of hydatidiform mole or chorionepithelioma, it is considered that this explanation need not invalidate the known facts in any way.

Relationship Between Previous Pregnancy and Chorionepithelioma

It would appear from the literature that the condition of chorionepithelioma most frequently follows hydatidiform mole, next most frequently, abortion, and least commonly, full-time pregnancy. It is not clear what is the evidence for the abortions which are reported in many instances: it seems at least possible that some of these "abortions" may in fact have been early hydatidiform moles, as the symptoms of both are, to

a lay person, indistinguishable: irregular bleeding following a period of amenorrhoea.

Whilst it is appreciated that it would be absurd to draw any conclusions from a single case, the sequence of events in the case reported above has led to an examination of the relationship of hydatidiform mole to chorionepithelioma and with both to pregnancy. It is extremely difficult to imagine in the reported case, that the original molar pregnancy existed even in fragmentary form throughout the succeeding pregnancy, to develop later into a chorionepithelioma of the uterus.

This in turn leads to a consideration of whether in fact there need be a straightforward progression from hydatidiform mole to chorionepithelioma, or whether each condition may not arise separately, de novo, from different ova, and at different times.

It might appear at first that those cases where the chorionepitheliomatous change had occurred very shortly after the completion of a full-time pregnancy would not fit this theory. It should be remembered that cases have been reported where vesicular pregnancy and even chorionepithelioma has developed side by side with a normal pregnancy (Brews, 1936; Waters and Crunden, 1943; MacRae, 1951; Rose, 1952). It is possible therefore that the trophoblast responsible for the growth of a chorionepithelioma may originate from a separate ovum.

Novak (1950) has drawn attention to the fact that chorionepitheliomatous tissue may develop long after the termination of the nearest preceding pregnancy. While allowing that there may have been an unsuspected intervening pregnancy, he contends that there may be in individuals an inhibiting factor which, while acting, prevents the development of carcinomatous changes, but, with its removal, the tissues are free to develop malignant changes.

Normal trophoblast occurring in conjunction with a full-time pregnancy is an ephemeral tissue; it is redundant after the termination of a pregnancy, and in the vast majority of cases is discarded after not more than 9 months. It is noted that most cases of chorionepithelioma run a rapidly fatal course, seldom more than 12 months from the time of cessation of any preceding hydatidiform mole, abortion or full-time pregnancy (Park and Lees, 1950). It may be argued from this that, where a case of chorionepithelioma develops after a longer interval, there is a likelihood of fresh trophoblast from a later source being the responsible agent. There would then be a pattern of behaviour which would conform to that of the more usual type of case. It is submitted that this explanation is at least as reasonable as the supposition that trophoblastic tissue can remain dormant in the body for years, in an inert form, becoming activated later by some unknown stimulus, or the removal of a hypothetical repressing agent.

Summary

(1) A case is described illustrating an unusual sequence of events: hydatidiform mole, followed by normal pregnancy, followed by chorionepithelioma of the uterus.

(2) The theory of origin of hydatidiform molar change and chorionepithelioma is discussed, and a new suggestion put forward to explain the many abnormal or anomalous cases recorded in the literature.

My thanks are due to Professor W. I. C. Morris for much encouragement and patient help in the compilation of this article. Also the Staff of the Medical Library of Boots Pure Drug Company, for their assistance in searching the literature.

References

Brews, A. (1936): *Proc. R. Soc. Med.*, **28**, 1213.
Brews, A. (1939): *J. Obstet. Gynaec. Brit. Emp.*, **46**, 813.
Freeth, D., and McCall, A. J. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 757.
Freund, E. (1929): *Frankf. Z. Path.*, **38**, 313.
MacRae, D. J. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 373.
Madden, S. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 68.
Marchand, F. (1895): *Mschr. Geburtsh. Gynäk.*, **1**, 419.
Mathieu, A. (1939): *Int. Abstr. Surg.*, **68**, 52, 181.
Novak, E. (1947): *Gynecological and obstetrical pathology*. 2nd ed. Saunders, Philadelphia.
Novak, E. (1950): *Amer. J. Obstet. Gynec.*, **59**, 1355.
Oliver, H. M., and Horne, E. O. (1948): *New Engl. J. Med.*, **239**, 14.
Park, W. W., and Lees, J. C. (1950): *Arch. Path.*, **49**, 73, 205.
Pick, L. (1904): *Berl. klin. Wschr.*, **41**, 158.

Rose, E. M. (1952): *Brit. med. J.*, **1**, 1285.
Schlimovitz, N., and Van Brown, D. (1950): *Surgery*, **28**, 755.
Schumann, E. A., and Voegelin, A. W. (1937): *Amer. J. Obstet. Gynec.*, **33**, 473.
Simard, L. C. (1937): *Amer. J. Cancer*, **30**, 298.
Thomas, R. C. (1934): *Brit. med. J.*, **2**, 590.
Walsh, C. H. (1935): *J. Obstet. Gynaec. Brit. Emp.*, **42**, 194.
Waters, E. G., and Crunden, A. B. (1943): *Amer. J. Obstet. Gynec.*, **46**, 299.
Zalka, E. de (1928): *Amer. J. Path.*, **4**, 59.

THE VERTEBRAL VENOUS DRAINAGE OF THE PELVIS

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S.E., F.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Liverpool

IN discussions on the origin of islets of endometrioma in parts of the body such as the pleura and arm, on the occurrence of malignant metastases in the spine or in remote areas such as the brain when a primary growth is in the pelvic organs, and on similar problems, the question of blood stream spread through the vertebral veins, the heart and lungs being by-passed, is frequently mentioned. The idea has generally been received with a degree of scepticism by gynaecologists, although a venous connexion between some of the pelvic organs and the ascending lumbar veins and their tributaries is recognized by anatomists. Their concept is illustrated by Figs. 1 and 2 which are based on diagrams published by Charpy (1898), Robinson (1949), and in *Gray's Anatomy* (1923).

In these diagrams it will be seen that outside the vertebral column is a venous network distributed mainly as an anterior plexus on the front of the vertebrae, and a posterior plexus on the laminae and spines. These communicate freely and over the lower part of the vertebral column are linked by ascending lumbar veins one on each side. These latter connect with the common or internal iliac veins and a presacral plexus of veins, including the middle sacral vein, at their lower ends, and ascend to become the azygos vein (on the right) and the superior hemiazygos vein (on the left). The external vertebral plexus, which drains ultimately into the superior vena cava, also anastomoses freely with an internal vertebral plexus which lies within the vertebral canal between the dura mater and the vertebrae and receives tributaries from the bones and the spinal cord. The plexus extends the whole length of the canal and communicates directly or indirectly with various veins of the trunk, arms, head and neck. The main links between the internal and external

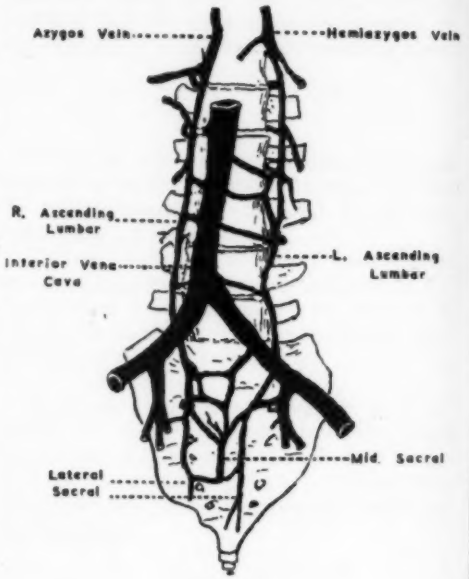


FIG. 1

The lower part of the anterior external vertebral venous plexus.

vertebral veins are the intervertebral veins which pass through the intervertebral foramina. Although the whole of this venous system is subject to many variations in detail, it is fairly constant so far as the essential features are concerned and it does provide a theoretical pathway from the pelvis to other parts of the body which is not interrupted by the lungs. Its existence has long been recognized but during the last 100 years interest in it has centred mainly on its function as a collateral pathway for blood from the pelvis and legs when the inferior vena

cava becomes obstructed by disease or by operation. A review of the literature bearing on this aspect was published in 1949 by Robinson and it is now generally accepted that the lumbar veins serve as one of the main routes for blood when the inferior vena cava is obstructed either in man or animals. Any argument which remains is concerned with their function when the caval circulation is intact.

In this connexion Batson (1940) experimented on two live monkeys, injecting radio-opaque material into the dorsal vein of the penis and showing that, although this ordinarily passed into the vena cava, it could, under certain conditions such as increased intra-abdominal pressure, be seen to pass into the vertebral veins and their connexions. He also obtained similar results by experiments on the human male cadaver and concluded that the vertebral system consists of valveless veins which carry blood at low pressure and in which the flow is sometimes arrested or reversed. Batson proved to the satisfaction of most authorities that the vertebral veins and plexuses could provide a route for the transfer of malignant cells from a primary growth in the pelvis to form metastases in the spine or in remote areas such as the brain, at the same time sidetracking the caval, pulmonary and portal systems. Batson's experiments were restricted to the male but it is generally assumed that the results are applicable to the female. Nevertheless, so far as I know, the actual passage of blood and other material from the uterus to the vertebral plexus in a live woman with a normal circulation has not previously been demonstrated, and it is for this reason that a record of its accidental happening during hysterosalpingography is here reported.

Intravasation is a not infrequent complication of hysterosalpingography although it can be overlooked unless the patient is screened during injection of radio-opaque material. Even if it is seen it is not always possible to take a radiograph as a permanent record because, once in the bloodstream, the material disseminates rapidly. If it enters lymphatics and reaches lymph nodes it remains for a longer time (Kika, 1954). According to Davids (1953) intravasation occurs in 2 per cent cases of hysterosalpingography, while Kika (1954) noted it in more than 4 per cent sterile women investigated. In the experience of our unit and despite taking all possible precautions against it, it occurs in not less than 1 per cent cases but our records are not sufficiently complete to enable an exact assessment. When intravasation does occur the medium is usually seen to leave the pelvis either by the ovarian veins (Figs. 3, 4, 5) or, more commonly, by the iliac veins (Figs. 5, 6) and illustrations of these kinds are commonly published. It may be that if the radio-opaque material enters the veins at the fundus it is more likely to be conducted away by the ovarian veins, whereas if it enters at a lower level in the uterus it is more likely to drain through the internal iliac veins.

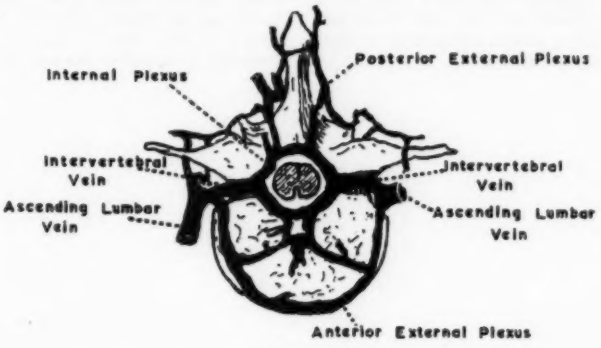


FIG. 2

The internal and external vertebral venous plexuses.

By chance one case of intravasation in our series showed a third method of venous drainage —through the vertebral plexus (Fig. 7). It so happened that in this case there was a hold-up at the inner ends of the tubes and the break into the circulation occurred at the level of the cervix; this may or may not be significant. In the radiograph (Fig. 7) the radio-opaque material can be seen in the venous plexuses* in the bases of the broad ligament and the paracolpos and, on the right side and less definitely on the left, there is a suggestion that it may be in one or other branch of the internal iliac vein. From here, however, it appears to enter the ascending lumbar veins on either side and also shows up clearly the window-like pattern of the pre-sacral venus plexus. Moreover, from the ascending lumbar veins it is possible to see the shadows of two of the intervertebral veins on both sides, and this means almost inevitably that the medium obtained access to the internal vertebral plexus. The possibility of the cross veins of the anterior external lumbar plexus lying in front of the bodies of the vertebrae being mistaken for intervertebral veins is discounted because the shadows are situated exactly opposite the intervertebral foramina in each case. The position of other tiny collections of radio-opaque material seen overlying the shadows of the vertebrae cannot be determined—it might be in any of the small venous channels within or without the vertebral column.

After this experience other radiographs showing intravasation taken from our own series and from those published by others have been studied for signs of the vertebral veins. On several it is possible to see globules of radio-opaque material which *might* be in this system (e.g., Figs. 4, 5 and 6) but in none is the evidence convincing. In the one case illustrated in Fig. 7, however, there can be little doubt and in this the radiographic appearance of the vertebral plexus agrees remarkably well with that described and illustrated by anatomists (Fig. 1) and would appear to afford conclusive evidence that, even in the reasonably normal woman, some parts of the uterus at least can drain into the external and internal vertebral venous channels. Moreover, in this case the woman was resting quietly on her back and, so far as can be ascertained, suffered no increase in intra-abdominal pressure such as was necessary to produce vertebral venous drainage of the male pelvic organs in Batson's experiments on monkeys. The experience goes to substantiate the probability of this route being sometimes used for the spread of tissue cells, blood clot and organisms from the pelvis to remote parts of the body.

* Some of the fine ramifications around the cervix and vagina may be lymphatics, although the rapidity with which they cleared suggested that most were blood vessels. The larger vessels are certainly veins and emptied so quickly that a second injection of medium was made to secure the radiograph.

References

Batson, O. V. (1940): *Ann. Surg.*, **112**, 138.
Charpy, A. (1898) *in* Poirie and Charpy: *Traité d'anatomie humaine*. Tome II, Fasc. III, p. 1066. Masson, Paris.
Davids, A. M. (1953): *Amer. J. Obstet. Gynec.*, **65**, 1167.
Gray's Anatomy (1923): 22nd edition by R. Howden. Longmans, Green, London.
Kika, K. (1954): *Amer. J. Obstet. Gynec.*, **67**, 56.
Robinson, L. S. (1949): *Surgery*, **25**, 329.

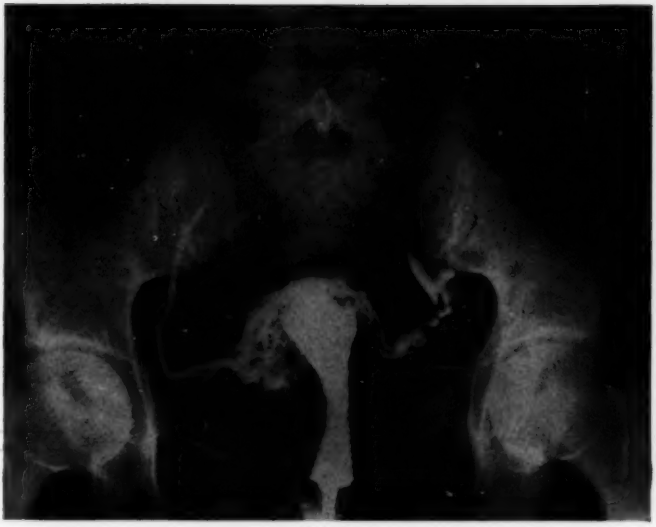


FIG. 3

Fundal intravasation with conduction of the material away from the pelvis by what are considered to be the ovarian veins, although this is not certain.

FIG. 4

Drainage of intravasated material via the left ovarian vein.

FIG. 5

Intravasated material showing the pampiniform plexus, the ovarian, uterine and internal iliac veins, and probably the right common iliac vein and the inferior vena cava.

FIG. 6

Intravasation with conduction of the material via the internal and common iliac veins.

FIG. 7

Intravasation. The radio-opaque material enters the blood stream at level of the cervix and passes into the ascending lumbar, intervertebral and pre-sacral veins. Compare this with Figs. 1 and 2.

MONO-AMNIOTIC TWIN PREGNANCY

Two Cases

BY

GORDON M. PARKIN, M.B., B.S., D.G.O.(Syd.)

Clinical Superintendent, King George Fifth Memorial Hospital, Sydney

MONO-AMNIOTIC twin pregnancy is a rarity which, however, may not be discovered unless the placenta from each case of twin pregnancy is carefully examined. In 1935, Quigley published a comprehensive review of the subject, in which he had collected 109 cases from the world literature. Since that time a further 30 cases have been recorded. There are only 14 cases recorded in English and American literature.

The 2 cases reported here occurred within 8 days. It has always been a routine at this hospital to carefully examine the placenta in cases of twin pregnancy, or other multiple pregnancy, and these cases are the first to occur at this hospital.

CASE REPORTS

The first patient was aged 24 years. One previous pregnancy had been a tubal gestation, and salpingectomy was carried out. Her last menstrual period had been on 20th September, 1953. This pregnancy advanced satisfactorily until the 33rd week, when multiple pregnancy was suspected, and subsequently confirmed radiologically. A mild degree of pre-eclamptic toxaemia necessitated the patient's admission to hospital at the 37th week, and labour was induced 10 days later by stripping of the membranes and pitocin injections. Both foetuses were presenting by the vertex. Labour progressed satisfactorily and, after 11 hours, the presenting vertex was at the perineum. Pudendal nerve block anaesthesia was carried out, and the presenting vertex was delivered spontaneously. After delivery of this head, a loop of umbilical cord was found to be twisted about the baby's neck. This was readily slipped over the head, and delivery of the first child completed. It immediately became apparent that the loop of cord which had been around the baby's neck was not associated with this child's umbilical cord, and therefore represented the prolapsed cord of the second child. Vaginal examination was carried out immediately, and the second twin found to be presenting by the vertex, which was engaging in the brim. The cord was pulsating slowly. The second twin was therefore immediately delivered, quite easily, with forceps. Neither infant presented any difficulty with resuscitation, and their condition remained good. The placenta was delivered by abdominal pressure.

The placenta was a single placenta, showing no suggestion of division into two parts. On examination of the foetal surface (Fig. 1) the two cords were inserted close together, with a number of anastomoses between their vessels. No evidence of any remnant of membrane could be found between the insertions, and, in fact, there was a shallow, approximately circular depression, free of vessels, between the insertions. The two cords were entwined about each other, but no true knots were present.

The infants, both male, weighed respectively 6 pounds 4 ounces, and 5 pounds 2 ounces. Their blood groups were identical, as far as examined—A, Rh+ve, cDE/cde (R2r), M, S. The babies were X-rayed to determine the possible presence of situs inversus, but this was not found.

The second patient was a primipara, aged 20 years. Her last menstrual period was on 30th November, 1953. Her pregnancy advanced satisfactorily until the 33rd week, when she was admitted to hospital on account of pre-eclamptic toxaemia. A twin pregnancy was confirmed radiologically. Six days after admission the membranes ruptured spontaneously and the patient came into labour. The labour was normal,

and after 12 hours the presenting vertex was at the perineum. Pudendal nerve block anaesthesia was employed, and the first twin was delivered instrumentally on account of its small size. After delivery of the first child, abdominal examination revealed that the second twin was presenting by the vertex, and the foetal heart sounds were quite slow—80 per minute. Vaginal examination was performed immediately, and the second vertex was found to be engaging in the brim, no second bag of forewaters being felt. Delivery of the second twin was therefore effected by forceps. Neither twin caused any concern after delivery, and they remained good. The placenta was delivered by abdominal pressure.

On examination, the placenta was single, without evidence of separation into two parts. The cords were inserted close together, with numerous anastomoses between their vessels. The two cords were knotted together in two places, as can be seen in the photograph (Fig. 2).

The infants, both male, weighed respectively 4 pounds 8¼ ounces, and 3 pounds 15¼ ounces. Their blood groups were identical, as far as examined—A, Rh+ve, anti-c +ve, MN, S -ve, Tj(a) +ve. They progressed satisfactorily.

Comment

The occurrence of mono-amniotic twins does not give rise to any increased risk to the mother. Even though it might be thought that interlocking of the twins might occur during labour, this has not occurred in any of the recorded cases. In Quigley's series there were 5 maternal deaths, 4 due to eclampsia, and 1 due to central placenta praevia. These conditions could not be ascribed to the fact that the twins were mono-amniotic.

However, there is a very large risk to the foetuses. In Quigley's series, the foetal mortality was 68 per cent and in only 15 per cent of cases did both twins survive. This high incidence of foetal mortality is due almost entirely to the frequency of knotting and intertwining of the cords. The foetuses frequently succumb before the onset of labour, but may also succumb during the course of labour. In the two cases reported here, delay in delivery of the second twin would very probably have resulted in its death.

Reference

Quigley, J. K. (1935): *Amer. J. Obstet. Gynec.*, **29**, 354.

References to Further Reported Cases

Boyle, J. B., and Richter, C. F. (1947): *Amer. J. Obstet. Gynec.*, **53**, 886.

Coulton, D., Hertig, A. T., and Long, W. N. (1947): *Amer. J. Obstet. Gynec.*, **54**, 119.

Frewer, E. (1936): *Brit. med. J.*, **1**, 159.

Henderson, J. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 921.

Jones, W. E. (1942): *Amer. J. Obstet. Gynec.*, **43**, 130.

King, J. A., Herring, J. S., Witt., E. D., and Blood, B. (1952): *Amer. J. Obstet. Gynec.*, **63**, 691.

Litt, S. E., and Strauss, H. A. (1935): *Amer. J. Obstet. Gynec.*, **30**, 728.

Parks, J., and Epstein, J. R. (1940): *Amer. J. Obstet. Gynec.*, **39**, 140.

FIG. 1

The foetal surface of the placenta from the first case.

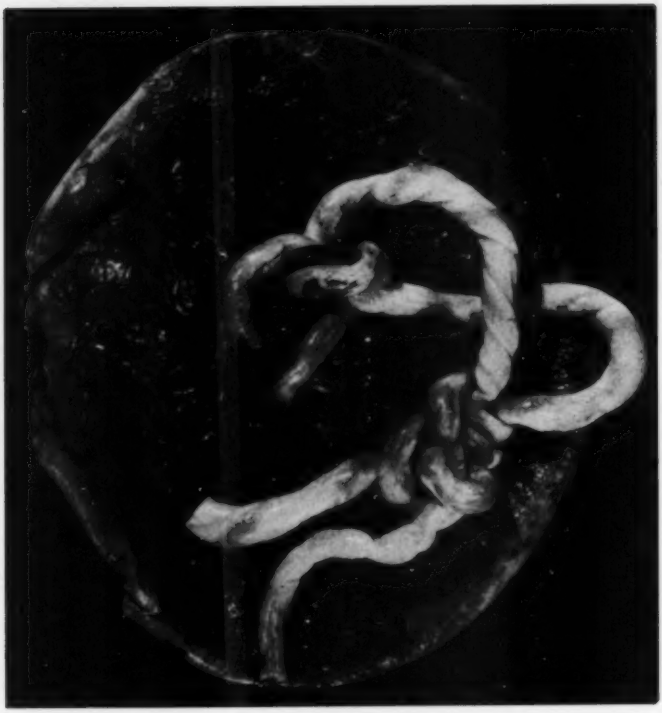


FIG. 2

The foetal surface of the placenta from the second case.

THE RURAL SCENE SURVEYED*

An Obstetrical Review

BY

R. F. LAWRENCE, E.R.D., M.D., M.R.C.O.G.

Consultant Obstetrician

Boston General Hospital, Holland County Council

INTRODUCTION

IF the first part of my title evokes pictures of William Cobbett riding round the shires on horseback in the early nineteenth century, or even of Alexander Selkirk in remote solitude on the island of Juan Fernandez, I hope the second half of the title will act as a corrective.

The idea for this paper came into my mind when I had been studying a number of medical reports from maternity hospitals, and annual reports of local health authorities. It seemed that the maternity hospital reports gave detailed accounts of the unusual and exceptional cases, without relating them to the material from which they were selected or the conditions under which they occurred. Local authority reports, on the other hand, gave statistical data with some scanty background information but hardly any clinical facts. These two groups of reports therefore seemed to be neither complementary nor supplementary: together they failed to give a clear picture of the work of the maternity services as a whole.

I am in the rather unusual position of being the only obstetrician working in the administrative county in which my main hospital is situated. There are few obstetric units near enough to attract patients outside the county boundaries, and the movement of patients within the county is almost entirely towards the centre. I am, therefore, able to see most of the hospital cases, whether booked or not booked, as well as keeping in close touch with the domiciliary work by virtue of my appointment as Consultant Obstetrician to the County Council. It seemed that I might be able to survey the work of the maternity services of the county and give a more complete picture than could be obtained from other sources.

This report concerns the year 1951, chosen because it was the first full year for which figures were available, and also because census figures for that year were available.

GENERAL INFORMATION

The Holland parts lie in the south-east of the County of Lincolnshire, and are bounded on the north by the parts of Lindsey, on the west by the parts of Kesteven, and on the south by Rutland, Northamptonshire, Cambridgeshire, and Norfolk. Its area is 267,849 acres, and the greater part of the land surface averages 1½–5½ feet below the level of high water at spring tides. It is essentially an agricultural county, consisting almost entirely of arable land; of the total area 89·6 per cent is taken up with agriculture in one form or another. There are, in addition to large farms, about 4,000 farm units of less than 50 acres, and of these about one-third are less than 5 acres; the average size of the holdings is 47 acres. The population is 101,545 and, with the exception of Boston and Spalding, which have respectively 24,000 and 14,000 inhabitants, is evenly distributed throughout the rural area. Forty-six per cent of the population are engaged in agriculture, 42 per cent in services (i.e., building, commerce, administration, and the professions) and only 12 per cent in manufacture.

The community pattern is quite unlike that in most rural areas in the country, and is even unlike those of the immediately adjacent counties of Lindsey and Kesteven. Its peculiarity

* Communicated to Meeting of North of England Obstetrical and Gynaecological Society, 19th November, 1954.

may be attributed to the unusual physical conditions which have prevailed since the establishment of the earliest settlements, and also to the extremely high productivity of the land. The nucleated type of settlement grouped round the church is not common in the county, and is only found in the urban centres. Elsewhere the community pattern is rather one of linear development along the existing highways, the villages sometimes extending to two or three miles in length without any definite centres.

Medical Services

There are 38 general practitioners resident in the county, and 22 practitioners living outside come into the county to attend patients. There are 672 hospital beds, of which approximately 250, constituting all the "acute" beds available, are in Boston. There are three maternity units, of which two, with 33 beds, are in Boston, and one with 12 beds in Holbeach. There are no general practitioner maternity beds. Apart from the hospital staff, there are 6 district midwives, 20 midwives who are also district nurses, and 10 health visitors under the supervision of the Chief Nursing Officer and Supervisor of Midwives with 4 assistants.

Reproductive Data

There were altogether 1,719 births in the County during 1951. The census figures show that there were 21,600 females between the ages of 15 and 44. This gives a reproductive rate of 8 per cent, i.e., practically 1 in 12 of the females of reproductive age gave birth to a child in the year.

Of the 1,719 births, 1,671 were live births and 48 were stillbirths. This gives a live birth rate of 16·5 per thousand of the population, compared with 15·4 per thousand for England and Wales. The stillbirth rate was 22 per thousand live and stillbirths compared with the national figure of 23. There were 2 maternal deaths, giving a maternal mortality rate of 1·16 per thousand total live and stillbirths, compared with 0·65 per thousand for the country as a whole. The infant mortality rate, i.e., deaths of infants under one year of age per thousand births, was 29·2 as compared with 35·8 for the previous year. The national figure was 29·6.

Baird has reminded us that reproduction is fundamentally influenced by heredity but is also greatly affected by custom, tradition, standards of education, and economic factors. These considerations must not be overlooked in assessing our results.

Racially there is a strong element of Scandinavian or Teutonic ancestry, and as a result there is a preponderance of large boned, heavily built females, and the small pelvis is rarely met with. The inhabitants are firmly attached to the land, and there is little movement of "foreign" blood into the area. In this closed community inter-marriage is frequent, and certain hereditary defects are more than usually common. An instance of this is retinitis pigmentosa, which is traceable back to "Blind Tom" of Kirton who was well-known two hundred years ago. As in most primitive and agricultural communities, early marriage and large families are common. (I have myself delivered a woman of her twentieth child.)

Most of the women work on the land whenever work is available: they are accustomed to long hours and hard labour in the fields, but as they are generally well-nourished this results in a high standard of general health and hardiness. There is practically no alternative occupation and early marriage is regarded (not without pleasurable anticipation) as a girl's normal fate. There is, therefore, always a considerable number of young primigravidae of good stature and nutrition who can be expected to have uneventful pregnancies and normal confinements. There is a correspondingly small proportion of elderly primigravidae; those who bear their first child late in life do so because of late marriage rather than true infertility.

Educational and economic standards are improving but it is still not uncommon to find people who have never left their birth-place, and who have no interests beyond satisfying their most primitive instincts. Farming has in recent years brought prosperity to the area, and it is unusual to find a farmhouse or small-holder's cottage without a television set. This opportunity to develop an interest beyond the daily round of work may well have a very beneficial effect on the educational standard of the community.

Institutional Deliveries

Of the total of 1,719 deliveries, 928 or 53 per cent occurred in hospital. Hospital beds are reserved for patients coming within the following priority groups: (1) medical or obstetrical abnormalities, (2) difficult home circumstances, (3) primigravidae and multigravidae who have had 5 or more pregnancies. After the needs of these groups have been met, applicants not coming within these groups are accepted. All applicants must apply in person at one of the hospital clinics where they are seen by the Consultant Obstetrician or his deputy. Any patient applying on sociological grounds must support her application by a certificate of necessity from the County Medical Officer of Health, issued on the report of the Health Visitor.

Analysis of their social and economic status gave the following results:

		Per cent
Class I	Upper professional and managerial strata .. .. (Income above £2,000 per annum)	Nil
Class II	Managers, Employers, Professional .. (Income above £1,000 per annum)	1
Class III	Skilled and black-coated workers .. (Income above £500 per annum)	17·4
Class IV	Semi-skilled (including agricultural workers) .. .. (Income above £250 per annum)	78·3
Class V	Unemployed—problems	3·3

The accuracy of this classification is open to question, as the wages of agricultural workers are variable and, if allowance is made for the fact that earnings in kind are not included, the economic standard of class IV is probably much better than their monetary earnings imply. If the haemoglobin level is taken as a criterion, 71 per cent of the primigravidae and 66 per cent of the multigravidae, whose haemoglobin level was 80 per cent or over, must be accepted as of good nutritional state, despite the fact that almost 80 per cent of the patients delivered in hospital had an income of less than £500 per annum (Table I).

The principal clinical features are summarized in Table II. The most common cause of admission to hospital before labour was pre-eclampsia (with which is grouped non-toxaemic

Table I

Age at First Confinement

	Under 16	16–20	21–25	26–30	31–35	36–40	Over 40
Number	1	86	175	79	22	10	1
Percentage	0·3	23·0	46·8	21·1	5·9	2·7	0·3

Number of Previous Pregnancies (Excluding Abortions)

	0	1	2	3	4	5	6	7	8	9	10	11	12
Number	361	168	77	33	18	6	3	7	2	3	4	0	1
Percentage	52·9	24·6	11·3	4·8	2·6	0·9	0·4	1·0	0·3	0·4	0·6	0	0·1

Haemoglobin at First Visit (Sahli)

	Under 50	50–59	60–69	70–79	80–89	90–99	100 and over
Primigravidae							
Number ..	1	5	9	34	82	36	2
Percentage ..	0·6	3·0	5·3	20·1	48·5	21·3	1·2
Multigravidae							
Number ..	0	3	20	43	49	23	11
Percentage ..	0	2·0	13·4	28·9	32·9	15·4	7·4

hypertension) and ante-partum haemorrhage (16 cases diagnosed as accidental haemorrhage and 5 as placenta praevia). In general, labour caused little trouble: in 11 cases it lasted over

TABLE II

Condition	Booked	Not Booked	Total
Pre-eclampsia	52	13	65
Eclampsia	1	1	2
A.P.H.	12	9	21
Prolonged labour	10	1	11
P.O.P. and D.T.A.	19	—	19
Breech delivery	16	4	20
P.P.H.	28	4	32
Manual removal of placenta	9	1	10
Version before labour (G.A.)	22	—	22
A.R.M.	35	7	42
Caesarean section	7	4	11
Forceps delivery	42	1	43
Stillbirths	23	4	27
Neonatal deaths	15	5	20
Premature births	51	16	67
(died)	7	—	7

48 hours but ended spontaneously, while 43 cases required forceps and 11 Caesarean section. Surgical induction of labour was carried out in 43 cases, mainly on account of toxaemia and post-maturity. There were 2 maternal deaths. The first was an unmarried primigravida who was admitted after having 6 eclamptic fits at home. She was treated with morphine and magnesium sulphate but remained restless and had one further fit. Labour was terminated by forceps delivery of a stillborn infant, apparently full-time. The mother subsequently developed cyanosis with signs of pulmonary oedema and died 18 hours after delivery.

The second case was admitted to a hospital outside the County on account of twin pregnancy complicated by jaundice, vomiting, abdominal pain, rise in blood pressure, albuminuria and acetonuria. Labour was induced by rupture of the membranes; the first twin was delivered as a breech and was stillborn. The second was delivered by forceps. She had a severe post-partum haemorrhage, and died 5 hours after delivery. The cause of death was stated to be acute liver necrosis.

Both these must be regarded as avoidable deaths, the first due to inadequate antenatal care (she had complained of headache for a week before the onset of fits) and the second due to faulty obstetric management.

There were 27 stillbirths and 20 deaths in the neonatal period: of 67 premature babies, 7 died.

This table is based on the standard Maternity Hospital Report, and summarizes the clinical material in numerical form. Each individual will form his own impressions of the work carried out, but I myself have been impressed with the frequency with which I have been confronted by medical problems—the diabetics, the cardiac cases, and particularly the hypertensives, and how rarely purely obstetric questions have arisen. As far as my own work is concerned, I feel that the era of the Obstetric Surgeon has passed away and been replaced by that of the Physician-Accoucheur.

DOMICILIARY CONFINEMENTS

Seven hundred and seventy-two cases were delivered in their own homes. In 635 cases the midwife was booked to act as midwife, and 137 as maternity nurse. There were 48 midwives in the area who had notified their intention to practice: of these 17 were employed in hospital. The average number of cases among those practising outside hospitals was therefore 25. In addition to those booked for home confinement, the midwives employed by the Local Authority also attend those mothers who leave hospital before the fourteenth day of the puerperium. I have been unable to find out how many cases were actually delivered by a doctor, or how many cases were delivered by a midwife with the doctor in attendance.

I have been unable to obtain any further details about the amount of midwifery carried out by general practitioners. The number of cases for which payment is claimed indicates only the number who had at least the minimum antenatal and postnatal examination, and gives no indication of the number of women who were actually attended in labour. My own impression is that a very large proportion of cases were dealt with entirely by the midwife, the general practitioner being called only if she got into difficulties. In this respect the details of medical aid calls are of interest: there were

altogether 175 cases, of which 33 were antenatal, 86 intranatal, 21 postnatal, and 35 for paediatric conditions. The analysis is given in Table III.

TABLE III
Medical Aid Calls

a. *Antenatal*		c. *Postnatal*	
A.P.H.	5	Varicose veins ..	1
Abortion ..	6	Pyrexia	16
Albuminuria ..	6	Other conditions	4
Varicose veins ..	1		
Hypertension ..	9		
Other conditions	6		
	33		21
b. *Intranatal*		d. *Paediatric*	
Malpresentation	3	Prematurity ..	5
Retained placenta	3	Dangerous feebleness ..	8
Post-partum haemorrhage ..	12	Ophthalmia ..	17
Prolonged labour	9	Malformations ..	2
Ruptured perineum	57	Jaundice	1
Eclampsia ..	1	Other conditions	2
Other conditions	1		
	86		35

Illegitimate Births and the Pre-marital Conception Rate

There were 89 illegitimate live births within the County and 8 unmarried mothers living within the County were delivered elsewhere. The illegitimate birth-rate is therefore 58 per thousand live births. The corresponding figure for England and Wales is 48 per thousand live births. Figures kindly supplied by Dr. Warin of Oxford show rates for county boroughs ranging from 28 for Gateshead to 75 for Blackpool and Oxford, with Halifax and Nottingham close runners-up with 74. I was surprised that the County of Holland produced such relatively respectable figures, and therefore decided to investigate the pre-marital conception rate. All primigravidae attending hospital antenatal clinics were asked the date of marriage among routine personal details. During 1951 I collected adequate information from 522 primigravidae; of these 122, or 233 per thousand primigravidae, had missed one period or more at the time of marriage. This figure cannot be compared exactly with the Registrar-General's figures of deliveries occurring within 8½ months of marriage (77·33 per thousand total legitimate maternities for England and Wales, 82·22 per thousand for the North Midland Region) but it is certainly suggestive that pre-marital conception is much commoner in this part of the world than the figures for illegitimate births would suggest.

It is amusing to speculate on the cause. The county is rich in beautiful churches and ugly chapels, so there is no reason to believe that the tenets of the Christian faith are unknown. However, Henry the Eighth referred to "the rude commons of this most brute and beastlie shire in the whole realm". In a later age John Conington, a native of Boston who, as a classical scholar, ranks with Jowett and Bentley, refers to his native county as the Boeotia of England. The Oxford Dictionary describes Boeotia as a district of ancient Greece proverbial for the stupidity of its inhabitants, so perhaps in succeeding centuries there has been no marked improvement. There is a local legend that before the fens were drained the wild-fowlers forsook their miserable marshes and retired for the winter to the more attractive high ground of the Wolds. There they found a mate for the long winter months, and returned to the Fens in spring taking the woman with them only if they had demonstrated their fertility. A third explanation suggested is that this is really Stella Gibbons country, liberally endowed with Cold Comfort farms and inescapably exposed to the influence of the luxuriant sukebind.

Other Problems

If I have implied that purely clinical problems have been comparatively rare, I must emphasize that non-clinical problems have frequently arisen. There have been problems due to the fragmentation of the Maternity Service as a result of the National Health Service Act, which divides the responsibility for the maternity service between the General Practitioner, the Local Health Authority, and the Hospital Service. In addition there have been many problems arising from local conditions. First, the low standard of intelligence and education, and the lack of health propaganda in the out-

lying districts has meant that it has been difficult to ensure adequate attendance for antenatal care; this difficulty has been increased by the poor bus services in the rural areas—in the majority of cases there are no buses except on market day. Sociological problems are numerous, many being connected with housing difficulties: one woman aged 24 was living in a derelict farm shed at the end of a field bordered by a land drain which she would have to cross by rowing boat and then walk two miles to the nearest point to which a car could approach. Because she lived in the County, the Urban Authorities would do nothing to help to rehouse her, and because the husband worked in the town the Rural Authorities were equally unhelpful: she was eventually rehoused in the town, but still had difficulty in accustoming her half-wild children to town life. Another woman, aged 35, was having her tenth child. She lived in an outlying part of the Fen, and no home help would go, so the husband had to arrange to work in the fields near the house so that he could look after the children while the wife was in hospital. Other problems arise in connexion with mental defectives: a woman of 33 who was mentally deficient and almost blind had 9 children, but when sterilization was advised the husband refused. Another mentally defective woman had 8 children, all of whom had been removed and placed in children's homes. She kept the youngest child, and was supervised by the Health Visitor who attended daily.

Illegitimate children have also been frequent sources of trouble. In some cases the Almoner has been successful in bringing together the parents, and resolving the difficulty. In some cases the illegitimate child has been adopted by the grandmother—thus becoming the legal sister of her own mother, and also of her own uncles and aunts, and in addition becomes aunt to her own half-sisters and half-brothers: in a number of cases the grandmother has taken both mother and child into the home, and looked after the child while the mother earned her living. There were also a number of women who had had several illegitimate children: one woman had 6 illegitimate children by 3 different fathers and was at last thinking of getting married. As there will always be a lurking doubt of the sanity of these women, it is questionable whether the children are suitable for adoption, and their disposal still remains a problem.

Organization and Planning

From what has gone before, it will be clear that the problems of the situation are manifold and various, and that no single individual can hope by himself to solve them. The only hope lay in the combined efforts of all those engaged in maternity work. The difficulty lay in finding a method of bringing them all into harmonious collaboration. After some thought I suggested the formation of an Obstetric Advisory Committee. I invited the County Medical Officer of Health to discuss the project with me, and to enlist the support of the Public Health Committee, while I tackled the Hospital Management Committee. We were successful in persuading both committees to support the proposal. I therefore invited the Medical Officer of Health and the Supervisor of Midwives, representing the local authority element, to meet me and my two G.P. clinical assistants, representing the Hospital element, for preliminary discussions. We then decided to invite the Local Medical Committee to send two representatives, and later co-opted the Paediatricians whenever any relevant matter was under discussion. It was hoped that this Committee would deal with matters referred by both the Public Health and the Hospital Management Committee, as well as matters raised by the members themselves. There was inevitably some mutual suspicion, with a tendency to take sides on the question of Domiciliary versus Hospital delivery. As meeting followed meeting month after month, with ample opportunity to air views and grievances, this feeling has gradually become less marked, and there is now developing something which may well become a team spirit.

A list of some of the more important topics dealt with by the Committee may be of interest:

Records and interchange of information between the G.P., Local Authority, and Hospital.

Notification of booking by G.P., hospital and midwife.

Interchange of information about patients booked for hospital when antenataled by G.P. or Clinic.

Arrangements for blood investigation and issue of blood group cards.

Flying squad arrangements and arrangements for dealing with haemorrhage.

Memorandum for midwives on conduct of third stage, and use of ergometrine. This was also passed to the local Medical Committee for circulation to general practitioners.

Care of premature babies.

Antenatal exercises and prenatal training and education.

This shows, I think, how many matters of importance can be usefully referred to a committee such as I have described, and how it can help to improve working relations in the obstetric field.

This discussion relates to a region which is dull, flat, monotonous, and entirely devoid of any feature of interest. These characteristics are undoubtedly reflected in my words but even though unsuccessful I think the attempt to present a complete picture of the reproductive conditions of the area is worth making. Increasing movement within the population will make it more and more difficult in the future to make such a review. The woman whose recurrent abortion is treated in Manchester, the woman delivered in Liverpool, and the woman whose vulva is excised in Newcastle, may be one and the same individual, though appearing in the records and contributing to the clinical features of three different areas. It is therefore important to seize the few opportunities that remain of examining such self-contained areas of static population as the County of Holland. The value of epidemiological research in such areas has been demonstrated by Pickles. The natural history of obstetrical conditions may also be revealed under similar conditions.

I am indebted to Dr. J. Fielding, County Medical Officer of Health, and Miss K. Bally, Supervisor of Midwives, for most of the information about the domiciliary service, and to Dr. Alan Eckford and Dr. Patrick Coffey who compiled the hospital statistics.

OESTROGEN THERAPY IN MISSED ABORTION AND LABOUR

BY

R. H. MARTIN, M.B., Ch.B., M.R.C.O.G.

AND

D. N. MENZIES, M.B., Ch.B., M.R.C.O.G.

From the Department of Obstetrics and Gynaecology, University of Liverpool

THE use of oestrogens in the treatment of missed abortion and missed labour was first suggested by Robinson, Datnow and Jeffcoate in 1935. Evidence was then produced which seemed to indicate that when the foetus is dead but retained *in utero* the inhibitory effect of progesterone is absent. The prolonged administration of oestrogen may then so sensitize the uterus that it evacuates itself either spontaneously, or in response to oxytocics such as quinine and posterior pituitary extract. Further clinical trials resulted in a report by Jeffcoate (1940) on the use of oestrogens in 55 consecutive cases of intra-uterine death of the foetus. Oestradiol benzoate was used in the earlier cases in the series and stilboestrol in the later ones with similar results. The hormone was given regularly for 5 to 8 days and was immediately followed by a quinine and oxytocin induction if abortion or labour had not occurred in the meantime. The uterus emptied itself in 87 per cent of these cases, the interval between commencement of treatment and the expulsion of the products of conception averaging 4·2 days.

Following these reports the method was widely used and accepted as the standard treatment for these conditions. It was not always successful, however, and as time passed the number of gynaecologists who questioned its value increased rather than diminished. Moreover, as knowledge of the respective actions of oestrogen and progesterone increased, the theoretical basis of the treatment became less secure. In 1950 Jeffcoate emphasized that the early experiments had not been controlled, so in the investigation reported here, carried out at his instigation, an attempt was made to control the results.

MATERIAL

The investigation was carried out at the Liverpool Maternity Hospital where, during the last 3 years, induction of labour or abortion was attempted in 45 cases of missed abortion and missed labour. Two of the treated cases were used twice in that when one method of induction failed, another was tried, thus making a total of 47 experiments in treatment. In the majority the duration of pregnancy was more than 28 weeks at the time of foetal death.

During the same 3-years period there were a further 52 cases of intra-uterine death. These were also studied but no treatment was given in this group, and all aborted or went into labour spontaneously.

METHODS OF TREATMENT

Three lines of treatment were planned, only one of which was to be followed in any particular case and the choice was made in rotation as the cases were admitted. The three programmes were as follows:

1. Stilboestrol 5 mg. orally .. .. 4-hourly for 7 days
2. Progesterone 5 mg. intramuscularly .. 4-hourly for 7 days
3. Sodium citrate 2 gr. orally .. .. 4-hourly for 7 days

Sodium citrate was chosen because it seemed reasonable to believe that it had no effect on uterine action.

If labour or abortion had not started at the end of any one course of these treatments, quinine sulphate gr. 5 was given orally 3 times at hourly intervals. This was followed by intramuscular

injections of 2·5 units oxytocin at hourly intervals for 6 doses. If the pregnancy still remained *in utero* the whole course of treatment was repeated. It is recognized that so far as oestrogen is concerned heavier doses are employed in many centres, but this experiment was planned to conform to the one on which the original claims were based.

Choice of the method of treatment strictly by turn should have resulted in an equal number of cases in each group. In fact more patients received oestrogen than either progesterone or sodium citrate because, with a large and ever changing junior medical staff, a "stilboestrol induction" was sometimes automatically ordered before it was realized or remembered that this controlled investigation was in progress. There were also 2 patients in whom an oestrogen induction was attempted and failed, who subsequently received progesterone in the one case, and sodium citrate in the other.

Assessment of Results

The treatment was recorded as successful if the uterus emptied itself during or within 48 hours of concluding the two courses of treatment. Induction failed 10 times in 9 cases, 3 patients ultimately requiring curettage, 4 being treated by artificial rupture of the membranes, and 1 by abdominal hysterotomy. In the remaining 1 a "failed" stilboestrol was followed by a "successful" progesterone induction.

Results

Forty-seven inductions were carried out on 45 patients and 52 cases were left untreated. The details of results are shown in Table I from which it will be seen that the overall success rate was 89 out of 99 (90 per cent). This is remarkably similar to the original 87 per cent success rate reported by Jeffcoate (1940) and suggests that the criteria adopted are comparable to those of the earlier investigation. However, the success rate with oestrogen was lower than with any other method of treatment, being 73 per cent as compared with 78·5 per cent and 91 per cent for progesterone and sodium citrate respectively. This suggests that stilboestrol has no advantage over an inert substance or over progesterone. Moreover, and bearing in mind that oestrogens have also been used to promote better uterine action in labour, it is interesting to note that the average duration of labour after stilboestrol induction (20 hours) was longer than that when progesterone (17 hours), sodium citrate (16·9 hours), or when no treatment was given (12·5 hours).

Table I

	Number of cases	Number successful	Average Interval. Induction-Delivery (days)	Average Length Labour (hours)
Stilboestrol ..	22	16	7·7	20·0
Progesterone	14	11(a)	10·8	17·0
Sodium Citrate	11(b)	10	6·4	16·9
No treatment	52	52		12·5

(a) Includes one success where treatment with Stilboestrol had already failed after one course.
(b) Includes one case where treatment with Stilboestrol had already failed after one course (and where Sod. Cit. also failed).

Further analysis indicates that parity did not materially affect the overall results, although the interval between the death of the foetus *in utero* and its delivery appeared rather shorter in multiparous women. Among the treated cases there were nineteen 1-gravidae, eight 2-gravidae, nine 3-gravidae, five 4-gravidae and six 5-gravidae. In these groups the average intervals were 30, 32, 15, 25 and 23 days respectively. However, the number in each group is small, and the average time is increased by those cases in which induction failed and which were ultimately terminated by surgery.

The cause of the intra-uterine death was known in only 22 cases. Four foetuses had gross congenital abnormalities and 4 had erythroblastosis. Of the remaining 14 deaths, 12 were associated with pre-eclampsia and 2 with postmaturity. The average intervals between intra-uterine death and expulsion of the products of conception were: 19 days in the toxaemia group, 12 days for the rhesus affected babies, and 18·5 days in the case of the abnormal foetuses. The 2 postmature infants were delivered on the seventh and fourth days respectively.

The duration of pregnancy at the time of the intra-uterine death apparently did not influence

the results in regard to either the outcome of treatment or the interval between death and delivery. Counting the whole series, treated and untreated, there were 12 cases in which the pregnancy died before the 28th week and 85 after that time. The difference in the results in the two groups is not significant and this is true whether or not the patients received treatment. In the small group of 4 untreated cases in which the foetal death took place before 28 weeks, the pregnancy appeared to be longer retained in the uterus than in those of the other groups (Table II).

TABLE II
Successful Cases. Influence of Maturity

	Intra-uterine Death—Delivery Interval (days)	
	Before 28 weeks	After 28 weeks
Stilboestrol ..	30·5 (4 cases)	22·5 (12 cases)
Progesterone	22·3 (2 cases)	22·4 (9 cases)
Sodium Citrate	8·2 (2 cases)	13·7 (8 cases)
No treatment	28·3 (4 cases)	14·0 (48 cases)

THE INTERVAL BETWEEN DEATH AND DELIVERY OF THE FOETUS

Probably one of the most important findings in this investigation pertains to the interval which usually elapses between death of the foetus and its expulsion. Foetal death *in utero* is ordinarily followed by abortion or labour within a few days. When it is not, however, as in the cases forming the subject of this communication, the interval approximates 21 days (Fig. 1). Moreover this interval is the same no matter whether the case is left untreated or whether induction is attempted by medical means (Table III), and

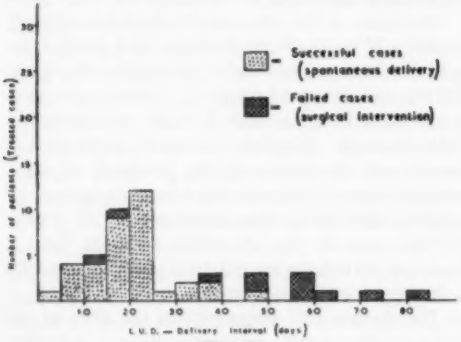

Successful cases (spontaneous delivery)
Failed cases (surgical intervention)
Number of patients (treated cases)
I. U. D. — Delivery interval (days)

FIG. 1

TABLE III
Successful Cases

	I.U.D.-Induction Interval (days)	Induction-Delivery Interval (days)	I.U.D.-Delivery Interval (days)
Stilboestrol ..	16·3	7·7	24·0
Progesterone	11·4	10·8	22·2
Sodium Citrate	9·2	6·4	15·6
No treatment			21·1

this is irrespective of the method of induction employed. Indeed it would appear that observations on the time elapsing between induction and delivery are potentially misleading, and that the interval between foetal death and delivery is more constant. This again confirms that stilboestrol, and indeed the other substances employed, played little if any part in determining the occurrence and time of abortion or labour.

It follows that, in practice, it is probably unnecessary, if not unwise, to offer any treatment until a dead foetus has been retained for longer than 3 to 4 weeks.

CONCLUSION

Although the number of cases treated in this series is small, nevertheless they do strongly suggest that neither stilboestrol nor progesterone has any particular merit when used in the treatment of missed abortion and missed labour. Moreover, they also suggest that quinine and oxytocin are equally valueless because their use did not materially shorten the interval between the diagnosis of intra-uterine death and the delivery of the foetus.

We are indebted to the members of the consultant staff of the Liverpool Maternity Hospital for allowing us to conduct this investigation on their patients and to record the results. In particular we are grateful to Professor Jeffcoate under whose direction and guidance this work was performed.

REFERENCES

Jeffcoate, T. N. A. (1940): *Lancet*, **1**, 1045.
Jeffcoate, T. N. A. (1950): *Proc. R. Soc. Med.*, **43**, 734.
Robinson, A. L., Datnow, M. M., and Jeffcoate, T. N. A. (1935): *Brit. med. J.*, **1**, 749.

RECURRENT VOMITING IN PREGNANCY

Three Cases of Hiatus Hernia

BY

D. F. P. GORDON, F.R.C.S.(Ed.), M.R.C.O.G.

Late Temporary Senior Registrar, North Middlesex Hospital

IT would seem that more attention has been paid to this condition in America although (most recently Dutton and Bland, 1953) reviews of cases are now beginning to appear in print in this country. It is difficult to find any reference to the statistical occurrence of the lesion in the English literature although Rigler and Eneboe (1935) in Iowa found a hiatus hernia present in 12 per cent of all patients attending their antenatal clinic.

I have confined my investigation to those cases of vomiting of pregnancy severe enough to demand admission, between May, 1953 and April, 1954. The investigation consisted of taking a close history with reference to heartburn, regurgitation and the relation to posture of these symptoms, and X-ray examination after barium swallow.

Of 10 cases so investigated, there was a hiatus hernia in 3 through the oesophageal hiatus, with oesophageal reflux. The commonly accepted aetiology of the condition is either trauma to the abdomen, in the non-pregnant patient, or congenital, in the same way that an inguinal or femoral hernia is congenital and it is presumed that increase of intra-abdominal pressure during pregnancy predisposes to the herniation.

Embryologically, the defect is due to the fact that the development of that part of the diaphragm which is derived from the dorsal mesentery and the mesoderm of the receding Wolffian body leaves not only a defect of varying extent in the muscular and tendinous structures, but also leaves a deformity in the conformation of the dome, possibly also resulting in a shortened oesophagus.

THE LITERATURE

Symptoms are manifold, but certain features seem common to all. All authors agree that posture influences the discomfort, that heartburn is a constant feature, and that all symptoms disappear after delivery.

Evans and Bouslog (1940) found a hiatus hernia present in all cases of heartburn in pregnancy. Haematemesis may also occur, and in one reported case (Diddle and Tidrick, 1941) death occurred from perforation of a high gastric ulcer into the mediastinum, although all admit that complications are rare.

Dutton and Bland refer to cases described by Vinson (1921) of oesophageal stricture following vomiting in pregnancy, and suggest that some of these cases were due to hiatus herniae.

CASE REPORTS

Case 1. Mrs. E. M. R. was a primigravida, aged 27, whose estimated date of delivery was 6th August, 1953.

On 27th January, 1953, she was referred as an emergency because of severe vomiting. She was very constipated, and after an enema the sickness settled down and she was soon discharged from the ward.

On 6th May, 1953, along with severe vomiting, she also complained of frequency of micturition and dysuria, and she was readmitted and treated as a urinary infection, although laboratory examination showed the urine to be sterile. She again settled down and was labelled as a neurotic type of vomiting of pregnancy.

She came under my care on 23rd May, 1953, when she was again admitted, being now approximately in her 30th week of pregnancy. Heartburn had been a constant feature for the past 2 months, this, along with her vomiting and upper abdominal discomfort, being worst at night and especially if she lay on her left side. Relief was obtained by propping herself up in bed, or by getting out and sitting in a chair. Antacids and histamine com-

pounds had little effect. A barium swallow showed a reducible para-oesophageal hernia, with reflux in the supine position (Fig. 1). Relief was obtained by causing her to sleep in Fowler's position and she was eventually able to tolerate a fat-free diet. Her condition was improved by these measures, although she was still vomiting when she was readmitted in labour on 14th August, 1953. Vomiting culminated in a haematemesis of 6 ounces just before the membranes ruptured, following which delivery was quick and easy. Agonizing heartburn was complained of immediately preceding the haematemesis. During the puerperium there were no untoward symptoms. A repeat barium swallow on 2nd September showed that neither hernia nor regurgitation was now demonstrable.

Case 2. Mrs. D. L. J., a 5-gravida, aged 38, with no history of any abnormality in her preceding pregnancies, attended the clinic at the 20th week of this pregnancy. Complaints of marked dyspepsia and regurgitation during the past 2 months were made along with copious vomiting on occasions, worst at night. Heartburn was present, along with lower substernal pain. Regurgitation was noticed if she bent down. Her sleep was always disturbed because of her desire to vomit. There was acetonuria, and her general condition was moderate. The tongue was furred and she stated that she had begun to notice tinglings in her fingers and toes recently. She was admitted and rectal fluids administered, since she could not tolerate anything by mouth. Sleep was obtained in Fowler's position and, with gradual improvement in her appetite and digestion, she slowly recovered.

Barium swallow on 14th July, 1953 showed a small reducible hiatus hernia (Fig. 2). She was at this time approximately 30- to 32-weeks pregnant. On discharge, she was advised to sleep with the head of her bed raised and to keep to a fat-free diet.

At subsequent attendances she still complained of heartburn and regurgitation, until, at her 38th week, she was readmitted because of haematemesis, along with her usual complaints of vomiting. With measures similar to those used before she again recovered, but since she was approaching term she was kept in the ward to await delivery, which was successfully accomplished a few hours after premature rupture of the membranes. The lying-in period and puerperium were devoid of incident.

One month after delivery a repeat barium swallow was performed, with the report "no further evidence of hiatus hernia".

Case 3. Mrs. E. B., aged 33, a 4-gravida, with no complaints during her last 2 pregnancies, first attended the clinic when she was 18-weeks pregnant, complaining of nausea in the mornings and sickness in the evening, along with heartburn. When next seen, one month later, she was still complaining and a barium swallow performed at this time showed no evidence of hiatus hernia, but marked lower oesophageal laxity with reflux in the supine position, which explained the complaint of heartburn.

Pregnancy continued similarly until, at her next visit, she complained that the vomit had been streaked with blood, and that unless she slept in a chair at night she did not get any relief at all from her vomiting. She was now at the 36th week of pregnancy. Heartburn was now worse than ever, and every time she bent forward her mouth filled with acid. She was admitted with acetonuria and a barium swallow examination now showed a large para-oesophageal hiatus hernia, along with oesophageal dilatation and oesophagitis (Fig. 3). She was allowed to sleep propped up on pillows, and with sedation and a fat-free diet the acetonuria disappeared and her general condition improved. A cultured specimen of urine was sterile and there was no albuminuria or hypertension at any time. She was discharged approximately a fortnight from term, and eventually underwent an uneventful spontaneous delivery.

The lying-in period was uneventful, apart from vomiting on one occasion. At the 10th day a further barium swallow examination showed that the hernia was still present, although smaller, but at her postnatal visit, one month later, no evidence was seen.

Seven other cases admitted to the wards in the early months of pregnancy as hyperemesis gravidarum of varying degrees of severity were also similarly investigated. None showed radiological evidence of a hiatus hernia, and in 6 no complaint of severe vomiting was ever made after control of the initial attack. The seventh case, Mrs. D.R.E. a primigravida, aged 23, started vomiting copiously again at her 32nd week of pregnancy and continued intermittently until term. All the symptoms and signs of a hiatus hernia were present but she refused to undergo an X-ray examination.

Discussion

The main symptoms of the lesion are heartburn and vomiting, influenced by posture, and in my cases the vomiting did not become noticeably worse as pregnancy progressed, but continued from the initial attack or recurred. This is at variance with most other published series. The heartburn bears no relation to the material swallowed and must be due to the concomitant oesophagitis.

The cause of the condition is obscure, but laxity of the tissues at the oesophageal hiatus seems to be the underlying factor, abetted during pregnancy by raised intra-abdominal pressure.

The treatment is difficult, but most relief is obtained by sleeping propped up in bed, along with efforts directed towards correction of the upset electrolytic balance.

FIG. 1
Case 1. Showing the bulbous herniation.

FIG. 2
Case 2. Showing the herniation lying alongside the oesophagus.

FIG. 3

Case 3. Showing the largest herniation, along with dilatation of the lower end of the oesophagus.

SUMMARY

A further 3 cases of hiatus hernia in pregnancy are reported.

The literature is briefly reviewed, and attention is drawn to the symptomatology and its relationship to the lesion.

My thanks are due to Mr. K. A. K. Hudson for his kind help in the preparation and review of these cases.

REFERENCES

Diddle, A. W., and Tidrick, L. (1941): *Amer. J. Obstet. Gynec.*, **41**, 317.

Dutton, W. A. W., and Bland, H. J. (1953): *Brit. med. J.*, **2**, 864.

Evans, J. R., and Bouslog, J. S. (1940): *Radiology*, **34**, 530.

Rigler, L. G., and Eneboe, J. B. (1935): *J. thorac. Surg.*, **4**, 262.

Vinson, P. P. (1921): *Surg. Gynec. Obstet.*, **33**, 412.

PREGNANCY COMPLICATED BY DIABETES

BY

G. O. RICHARDSON, M.D., M.R.C.P.

LINTON SNAITH, M.D., M.S., F.R.C.S., F.R.C.O.G.

AND

J. C. SIBLEY, M.D., M.R.C.P., F.R.C.P.(Can.)

Departments of Medicine and Obstetrics at the Newcastle General Hospital

IN pregnancy complicated by diabetes the value of continuous antenatal supervision at the hands of a single team, together with premature delivery, has been fully demonstrated (Peel and Oakley, 1949; Given *et al.*, 1950). Peel and Oakley showed that the foetal survival rate in a group of cases collected from 26 centres throughout Great Britain was 59·7 per cent whereas in their own series the survival rate was 75·1 per cent. Using similar methods, together with the use of substitutive therapy with stilboestrol and progesterone, White (1945) has recorded results with a foetal surviving rate approaching that of normal pregnancy.

The object of this paper is to record the results obtained in the pregnant diabetic patients attending the Newcastle General Hospital from 1947–1953, and to draw attention to the apparent differences in the foetal mortality rate in patients requiring insulin treatment compared with mild diabetics who are fully controlled without the use of insulin.

PATIENTS

Sixty diabetic women have been supervised during 74 pregnancies, including 2 cases of twins. For inclusion in the series either of the following criteria indicating diabetes was accepted.

(1) An authentic past history of diabetes requiring the regular daily use of insulin for control.

(2) The presence of diabetic symptoms together with either a fasting blood sugar of 180 mg. per cent or more, or a glucose tolerance test with a fasting level of 140 mg. per cent or more rising to over 200 mg. per cent and not falling below the fasting level plus 20 mg. per cent after 2 hours.

These rigid criteria have excluded a group of 7 patients who had symptoms of diabetes and abnormal glucose tolerance tests. These patients are discussed briefly below.

MANAGEMENT

Patients were seen at intervals not exceeding 2 weeks. At each visit weight and blood pressure were recorded and multiple urine samples collected the previous day were tested for albumin, acetone and glucose. Insulin dosage was adjusted so that the patient was kept free from diabetic symptoms and so that the urine contained no acetone and only minimal amounts of glucose. Protamine Zinc Insulin and soluble insulin were given simultaneously before breakfast, additional injections of soluble insulin being given if necessary. Toxaemic manifestations were treated by rest and a low sodium diet. Delivery was effected before the 38th week in most cases.

METHOD OF DELIVERY

There is general agreement that in primigravidae Caesarean section is the method of choice in the diabetic patient. It is also accepted that it is the method of choice in cases presenting obstetrical complications, which in a non-diabetic would permit a trial of labour. There is by no means general agreement concerning the method of delivery in cases where previous successful vaginal deliveries have occurred and

where diabetes is the only complication. Induction of labour is uncertain. Obstetrician, physician and paediatrician cannot all be in constant attendance. Moreover, when labour does commence it may be sufficiently prolonged to cause metabolic disturbance and render diabetic control difficult, and there is greater risk of injury to a premature foetus by vaginal delivery and a greater possibility of impacted shoulders if the baby is large. We now carry out Caesarean section for all primiparous women except when the diabetes is fully controlled without insulin and in whom the foetal head becomes deeply engaged and the cervix thinned out before the time for delivery has been reached. An exception is also made when premature labour occurs spontaneously and progress is rapid and uneventful. In multiparous women, since induction of labour is easier and the resulting labour shorter than in primiparous women, induction is done in all those with a favourable past history and where there are no obstetrical abnormalities. A past history of stillbirth or impacted shoulders is regarded as an absolute indication for Caesarean section.

Choice of Anaesthetic

In most cases undergoing Caesarean section local analgesia alone was used until the uterine peritoneum was incised, when it was supplemented by pentothal, nitrous oxide and oxygen in most cases. This probably diminishes the risk of foetal anoxia and makes establishment of respiration in the baby easier than with more prolonged general anaesthesia. In a few cases caudal analgesia alone was used and proved very satisfactory.

Results

No maternal death occurred in this series though one patient died a year later from miliary tuberculosis. One patient not included in this series was admitted as an emergency suffering from diabetic coma and was then found to be 6-months pregnant. She had not attended either the diabetic clinic or the obstetrical department. She died within 24 hours of admission. Autopsy showed that she also had bilateral bronchopneumonia and pyelonephritis. The total foetal loss of 16 included 5 abortions (1 therapeutic), 6 stillbirths and 5 neonatal deaths. Of the abortions 2 were associated with diabetic acidosis and one refused admission to hospital when bleeding occurred at the 23rd week. The therapeutic abortion was done for chronic renal failure with anaemia.

Of the stillbirths 2 occurred in patients with pre-eclamptic toxaemia, one of whom was also under treatment for a luetic infection, probably a major factor in the foetal death. In another gross hydrocephalus made craniotomy essential to effect delivery at Caesarean section. Two of the stillbirths which could probably have been prevented by early interference are referred to below.

There were 5 neonatal deaths. Hydramnios was present in 4 and toxaemia in 3 of the mothers, in one of whom pregnancy was deliberately terminated at the 32nd week to save the life of the mother. The child was extremely oedematous and showed respiratory distress, dying 24 hours later. In another spontaneous delivery occurred at 28 weeks. The child weighed 2 pounds 7 ounces and lived only 5 hours.

There were also 7 patients (see Table I) who did not fulfil the diagnostic criteria stated above. All had symptoms of diabetes during pregnancy with notably abnormal glucose tolerance tests. We have regarded these patients as suffering from pre-diabetes and they were treated with the same antenatal supervision and premature termination. This group appears to be similar to the 10 women with glycosuria and symptoms of diabetes during pregnancy recorded by Williams (1909).

Discussion

The total foetal mortality of 16 out of 76 and the mortality of 11 out of 71 viable pregnancies is similar to that recorded by Peel and Oakley (1949). The slight difference is not statistically significant. Included in this group are 13 women who had recently developed diabetes which was fully controlled without the use of insulin. These patients have been followed through 17 pregnancies without foetal loss. They were treated with the same degree of antenatal supervision as the patients requiring insulin and in most cases pregnancy was terminated prematurely, in several by Caesarean section. The

TABLE I

	Method and Time of Delivery in Weeks	Result	Weight	Glucose Tolerance Test Mg. per cent.	
E.L. 654	Induction 36	L.B.	7 lb. 6 oz.	120 : 165 : 205 : 165 : 115	Para 3(L.B.)
L.S. 757	C.S. 38	L.B.	8 lb. 7 oz.	107 : 180 : 205 : 150 : 112	Para 2(S.B.)
M.C. 1,396	Induction 38	L.B.	6 lb. 14 oz.	88 : 145 : 210 : 170 : 150	P.6 { 4 Ab. 1 S.B. 1 N.D.
C.L. 553	Induction 38	L.B.	7 lb. 1 oz.	85 : 140 : 230 : 180 : 140	Para 0
M.G. 1,136	Induction 40	L.B.	7 lb. 7 oz.	100 : 215 : 175 : 150 : 140	Para 0
M.C. 1,259	Induction 40	L.B.	6 lb. 13 oz.	90 : 205 : 230 : 200 : 175	Para 0
O.P. 1,333	Induction 38	L.B.	6 lb. 10 oz.	120 : 175 : 210 : 180 : 130	Para 0

difference in foetal mortality rate between insulin-requiring and non-insulin-requiring diabetics is statistically significant, and was entirely unexpected. It is usually considered that even in the pre-diabetic period the foetal mortality rate is considerably in excess of normal (Miller *et al.*, 1944), though a contrary view has been expressed by Imerslund (1948) and by Dolger and Herzstein (1944). Bass (1952) states that the foetal mortality rate is 4 times higher in mild diabetics not requiring insulin than in normal women.

Peel and Oakley reported a foetal mortality rate of 33 per cent among 42 non-insulin diabetics in the series collected from different centres in Great Britain, which was lower than that among the cases requiring insulin. Details of antenatal supervision and method of delivery were not given in these cases. On the other hand Given *et al.* (1950) found no such difference. It is not clear whether the antenatal supervision was similar nor whether premature delivery was carried out so frequently in the two groups. If it is confirmed that with similar treatment the mild non-insulin requiring diabetic has a significantly lower foetal mortality rate than has the patient requiring insulin, it indicates that comparison of the results obtained in different series is misleading unless each series is composed of comparable types of patient.

Reviewing the foetal deaths there are 3 in which a living child might have resulted from a more accurate assessment of the duration of pregnancy. Two stillbirths, being successive pregnancies in the same patient occurred when pregnancy was allowed to proceed to the 38th week in the mistaken belief that the foetus was small. One neonatal death also occurred owing to misjudgment of the foetal size. In this patient the pregnancy was interrupted too soon and it appeared that prematurity was the cause of death of the infant. Each of these 3 cases was complicated by hydramnios. In the whole series a major difficulty has been the determination of the real maturity of the foetus, the menstrual dates and the estimated size of the foetus, especially where there is hydramnios, often being unreliable. An accurate method of estimation of maturity would probably lead to a lower foetal mortality in pregnancy complicated by diabetes. In the present state of knowledge a foetal mortality rate of about 20 per cent appears to be unavoidable.

SUMMARY

(1) The results obtained in 74 consecutive pregnancies complicated by diabetes are reported.

(2) There is a significant difference between the foetal mortality rate in the non-insulin compared with the insulin-requiring diabetic. This indicates that comparison of results from different centres may be misleading.

(3) In order to achieve a high foetal survival rate it is essential to concentrate the care of the diabetic pregnancy into the hands of a single team. The difficulty in assessing the ideal time for delivery, particularly in patients with hydramnios, is a major factor influencing foetal survival.

References

Bass, M. H. (1952): *Advanc. intern. Med.*, **5**, 43.

Dolger, H., and Merzstein, J. (1944): *J. Amer. med. Ass.*, **125**, 931.

Given, W. P., Douglas, R. G., and Tolstoi, E. (1950): *Amer. J. Obstet. Gynec.*, **59**, 729.

Imerslund, A. O. (1948): *Nord. Med.*, **40**, 1880.

Miller, H. C., Hurwitz, D., and Kuder, K. (1944): *J. Amer. med. Ass.*, **124**, 271.

Peel, J., and Oakley, W. (1949): *Trans. 12th Brit. Congr. Obstet. Gynaec.* p. 161.

White, P. (1945): *J. Amer. med. Ass.*, **128**, 181.

Williams, J. W. (1909): *Amer. J. med. Sci.*, **137**, 1.

THE EFFECT OF HODGKIN'S DISEASE ON PREGNANCY AND FERTILITY

BY

H. G. FRANK, M.D., M.Rad.

Assistant Radiotherapist

Radium Institute, Liverpool

A SURVEY of the literature over the last 40 years shows that there has been a considerable difference of opinion on the effect of Hodgkin's Disease on pregnancy.

Some writers (Fabian, 1911; Klawans, 1942) have noted a rapid progression of the disease both during pregnancy and in the immediate post-partum period. Many other cases have, however, been reported (Minot and Isaacs, 1926; Gilbert, 1939; Goodman *et al.*, 1946; Jackson and Parker, 1947), in which the pregnancy did not affect the course of the disease or vice versa.

According to Gilbert (1951), these cases fall into three groups:

1. Pregnancy occurring during an active phase of the disease.
2. Pregnancy occurring during a dormant phase of the disease.
3. The disease appearing during pregnancy or the post-partum period.

He states that, in the first group, the pregnancy does not affect the disease. In the second, there are frequent relapses during the first 6 months of pregnancy and in the post-partum period but usually the pregnancy does not influence the course of the disease. In the third group, the disease is generally of an acute type. The response to radiotherapy is usually poor and the average survival from the onset of symptoms about 18 months or less.

With regard to treatment, he advocates that no active treatment be given unless absolutely necessary. If, however, the disease commences or recurs during pregnancy and treatment is considered urgent, e.g., for superior mediastinal obstruction, it is usually possible to carry out the treatment without affecting the child unless the pelvis is irradiated. In this case, spontaneous abortion usually occurs or the foetus is stillborn. He does not consider that therapeutic abortion is indicated, even in the third group, as ". . . in these cases the benefit one hopes for by interrupting the pregnancy is usually a vain hope".

Gemmell (1923a and b) found a history of oligomenorrhoea or amenorrhoea in some of his cases; also, that of 10 parous patients, 6 developed the disease during pregnancy. He states that 50 per cent of the women who develop Hodgkin's disease do so during periods of amenorrhoea, i.e., before puberty, after the menopause or during pregnancy. He put forward the theory that ovarian activity protects the patient against the disease and that it usually occurs when there is hypo- or non-function of the ovary. In substantiation of his hypothesis he cited the sex ratio (M : F=2 : 1). He concluded that oligomenorrhoea is associated directly with the disease and is not secondary to the concomitant anaemia. He advises termination early in pregnancy if the disease develops as he noted that pregnancy had a deleterious effect.

Bichel (1950), in a series of 81 patients, found 11 pregnancies—3 patients conceived twice and 4 patients once. They all produced full-time babies after a normal labour. There was no evidence of the disease in the children. The remaining patient died of the disease during the seventh month of her first pregnancy, the disease being very advanced before she became pregnant. In addition, spontaneous abortion occurred in 2 patients and a therapeutic abortion was carried out on 1 who developed the disease during pregnancy; in no case was the course of the disease affected. He concluded that, in his

series, pregnancy does not appear to have caused acute exacerbations nor accelerated the development of the disease.

The present series consists of 157 patients first seen during the years 1944–1949. Of these 105 were male and 52 female. Of the latter, 4 patients conceived—2 once and 2 twice. In 2 cases the onset of the disease occurred during pregnancy and in the other 2 it was quiescent at the onset of pregnancy.

Of the 2 patients who developed the disease during pregnancy, 1 has been recurrence-free for 2 years and the other has survived 7 years having had a second pregnancy with no ill-effects. Neither patient developed an acute type of disease which might have been expected according to the findings of Gilbert (1951). The other 2 patients both became pregnant during a quiescent phase of the disease and, although 1 developed a secondary anaemia, there was no evidence that the progress of the disease was accelerated by the pregnancy. The only patient who died survived for 5 years—considerably longer than the average for the whole series (3 years 8 months).

The patient who aborted spontaneously and later had a therapeutic abortion during a quiescent phase of the disease, suffered no ill-effects during either the pregnancy or the post-partum period.

It is interesting to note that in this series there were only 6 pregnancies in the 34 women of childbearing age (15–49 years)—a pregnancy rate of 3 per 100 per year with a live birth rate of 2 per 100, compared with 7 per 100 per year in the general population, according to the Statistical Review of the Registrar-General (1944–49, Table I). Whether this is due to impaired fertility in females suffering from Hodgkin's disease or to other factors, such as unwillingness to have children or a lower marriage rate, is an open question. Gemmell (1923a and b) has pointed out that some patients suffer from hypofunction of the ovary and this may have some bearing on their fertility.

With regard to the question of marriage, Gilbert (1951) advises against it. If, however, a patient marries, then he advises against childbearing unless the disease is limited to the cervico-thoracic region—a view with which Jackson and Parker (1947) and the writer concur. If, however, there is abdominal or pelvic involvement, childbearing is unlikely as an artificial menopause would be produced by X-ray therapy. If the ovaries have been irradiated but their function incompletely arrested, the patient should be advised against childbearing on the grounds that genetic changes have probably been induced by the treatment. These are irreversible, hereditary and always retrograde. The risk of spontaneous abortion is increased but, if a living child is born, it may be deformed. The genetic changes may not be apparent in the next generation but may appear in succeeding generations. It is of the greatest importance that this question should be discussed in detail with the patient's husband.

TABLE I

Number of Maternities and the Estimated Female Population between the Ages of 15–49 Years (Registrar General 1944–1949)

Year	Maternities in Thousands	Estimated Female Population in Millions
1944	763	11·5
1945	691	11·4
1946	833	11·4
1947	891	11·3
1948	784	11·25
1949	738	11·206
Total	4,700	68·056
Average	783	11·342

General Population

Average Maternity Rate = 7 per 100 females per year

Hodgkin's Disease

34 patients — 4 pregnancies, 2 abortions — 6

Average Maternity Rate = 3 per 100 females per year; 2 per 100 females per year (live births)

SUMMARY AND CONCLUSIONS

(1) A survey of the literature, together with the findings in the present series, is presented.

(2) It is doubtful whether pregnancy has any effect on the course of Hodgkin's disease. There

is, however, a risk that the patient's general condition may deteriorate during the course of the pregnancy unless precautions are taken. If the patient's condition is unsatisfactory and the disease becomes active, the prognosis may be poor as adequate treatment cannot be given.

(3) The cause of the lowered fertility in females suffering from Hodgkin's disease is not known but may depend to a certain extent on factors not connected directly with the disease.

(4) The advisability or otherwise of marriage of patients suffering from Hodgkin's disease is discussed.

Acknowledgments

I wish to thank Dr. J. S. Fulton, Medical Director of the Liverpool Radium Institute, for helpful advice and for the use of the records of the Radium Institute and Clinical Register. Acknowledgments are also due to my other medical colleagues for their assistance and cooperation.

References

Bichel, J. (1950): *Acta radiol., Stockh.*, **33**, 427.
Fabian, E. (1911): *Zbl. allg. Path. path. Anat.*, **22**, 145.
Gemmell, A. A. (1923a): *J. Obstet. Gynaec. Brit. Emp.*, **30**, 373.
Gemmell, A. A. (1923b): *Lancet*, **204**, 543.
Gilbert, R. (1939): *Amer. J. Roentgenol.*, **41**, 198.
Gilbert, R. (1951): *Acta radiol., Stockh.*, **35**, 71.
Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and McLennan, M. T. (1946): *J. Amer. med. Ass.*, **132**, 126.
Jackson, H., jr., and Parker, F., jr. (1947): *Hodgkin's disease and allied disorders*. New York: Oxford University Press. p. 91.
Klawans, A. H. (1942): *Amer. J. Obstet. Gynec.*, **43**, 895.
Minot, G. R., and Isaacs, R. (1926): *Amer. J. med. Sci.*, **172**, 157.
Registrar-General (1944–1949): *Statistical Review—England and Wales*. London: H.M. Stationery Office.

CHRONIC ENDOMETRITIS AND PLASMA CELL INFILTRATION OF THE ENDOMETRIUM

BY

J. M. BRUDENELL, M.B., B.S.

Research Assistant

Department of Obstetrics and Gynaecology, King's College Hospital, London

INTRODUCTION

THE histological diagnosis of chronic inflammation can readily be made in most tissues of the body but in the case of the endometrium certain difficulties arise. Proliferative changes are minimal, presumably because of the constant building up and breaking down of the endometrium under the influence of the ovarian hormones during the course of the menstrual cycle. Furthermore, in normal endometrium slowing of the blood stream through the coiled spiral arteries of the premenstrual endometrium leads to margination and emigration of leucocytes (Markee, 1940), and this cellular infiltration of the endometrium is increased during menstruation and may persist well into the follicular phase of the cycle. The almost complete absence of the plastic changes of chronic inflammation together with the normal occurrence of infiltration of polymorphonuclear cells, lymphocytes and macrophages has led to the plasma cell, by a process of elimination, acquiring a peculiar place in the diagnosis of chronic endometritis. In the interpretation of cellular infiltration of the endometrium the personal factor is important and may account in part for the considerable variation in the reported incidence of chronic endometritis, even in comparatively recent series of cases (1 per cent by Keene and Payne, 1934, 11 per cent by Sutherland, 1949).

The classical paper of Hitschmann and Adler (1907) established the conception of "glandular endometritis" as a normal menstrual phenomenon and restricted the diagnosis of chronic endometritis to an interstitial inflammatory process. These authors emphasized the importance of the plasma cell and indeed went as far as to make it the criterion for the diagnosis of chronic endometritis. They considered that plasma cells were invariably absent from normal endometrium and used this factor to differentiate between inflammatory and non-inflammatory lesions. Although this conception of the plasma cells as a *sine qua non* of chronic endometritis has been attacked by many writers since Hitschmann and Adler's paper, in general it may be said to have been accepted and at the present time plasma cell infiltration remains the basis on which a diagnosis of chronic endometritis is made.

In recent times the finding of small concentrations of plasma cells has been regarded as normal in many parts of the body.

In well fixed specimens the small intestine commonly shows a minor degree of plasma cell infiltration without any other evidence of a chronic inflammatory process (Magnus, 1954). Schiller (1948) reported the finding of occasional plasma cells in endometria which were apparently normal from every other point of view, whilst Dumoulin and Hughesdon (1951) emphasized that plasma cell infiltration of the endometrium is normally found after a spontaneous abortion or uncomplicated delivery. It is not clear for how long such an infiltration lasts but it presumably disappears when the normal menstrual shedding of the endometrium is resumed.

Tuberculous endometritis and malignant disease are commonly associated with heavy plasma cell infiltration whilst a variable degree of infiltration may occur in fibroid and adenomatous polypi and in metropathia haemorrhagia. In senile endometritis plasma cell infiltration is constantly found, but this condition is best considered as a separate entity apart from the

chronic endometritis occurring during the years between puberty and the menopause. In a consideration of the significance of plasma cell infiltration of the endometrium these conditions should accordingly be excluded and the diagnosis of chronic endometritis confined to those cases where there is no additional endometrial pathology. Especially is this so in cases of possible retained products of conception where degenerated chorionic villi or decidual reactions may easily be overlooked. In tuberculous endometritis Sutherland (1943) has shown that established cases may fail to show tuberculous lesions consistently, particularly in the type of tuberculous endometritis characterized by scanty tubercles in the endometrium with infiltration of the stroma by lymphocytes and plasma cells in moderate numbers. Where the chronic inflammatory reaction is very marked the tuberculous nature of the lesion may be masked.

Present Investigation

The present investigation was designed to examine the significance of plasma cells in the endometrium and their relation to chronic endometritis, bearing in mind that this term is used only to denote those cases not associated with other endometrial conditions mentioned above.

Material

The material consists of all routine endometrial curettings taken at this hospital during 1952 and 1953. Some of the specimens were obtained by formal dilatation and curettage whilst the remainder were taken with a Sharman endometrial biopsy curette. The majority of the material was premenstrual, and in the positive cases which were followed up repeat premenstrual biopsies were carried out at approximately 3-monthly intervals up to 1 year after the original section.

Staining Technique

Different authors have disagreed on the value of special stains to demonstrate plasma cells but most of the reported series have used the Methyl-Green-Pyronine method first introduced by Pappenheim (1899). To obtain successful results by this method immediate fixation in alcohol is necessary and even then, as is well known, results vary with different brands of pyronine used. In the present investigation the staining technique adopted was basically the Methyl-Green-Pyronine method of Trevan and Sharrock (1951), but differentiation and clearing of the material, which was fixed in 4 per cent formal saline, was carried out as recommended by Rosa (1950). Frequent control sections known to contain large numbers of plasma cells were stained and consistent results were obtained. Additional sections of both specimens were stained with haematoxylin and eosin. Although plasma cells are fairly readily identified when stained by the latter method it was felt that the special technique was of value in picking up small numbers of plasma cells. No difficulty was experienced in differentiating plasma cells from early decidual cells when stained in this way.

Results

The endometrium from 608 patients was examined, all cases of malignant disease, tuberculosis, polypi, metropathia and patients within 3 months of an abortion or full-time delivery having been excluded. Plasma cells were found in 46 sections, an incidence of 7 per cent. The positive cases were further subdivided into those cases showing a heavy infiltration of plasma cells and those in which only a few plasma cells were found in the whole section. At the start of the investigation an attempt was made to make a numerical assessment of the degree of plasma cell infiltration, but this failed to give consistent results when carried out by different observers or by the same observer looking at a given section on different occasions, and was eventually abandoned in favour of the arbitrary descriptive terms given above. Of the 46 positive cases, 5 showed a heavy infiltration of plasma cells, 10 showed moderate numbers of plasma cells and in 31 cases only a few plasma cells were found.

Heavy Infiltration by Plasma Cells

Five cases showed a heavy infiltration by plasma cells; of these only 1 was considered to be a true chronic endometritis. In this patient, in addition to a heavy infiltration of plasma cells, there was a great increase in the cellularity of the stroma due to the presence of large numbers of

TABLE I

Number of endometrial sections examined			608
Plasma cells present			46
Percentage incidence			7·6 per cent
Heavy Infiltration by Plasma Cells		Follow up	
Total number of cases .. 5			
Normal premenstrual endometrium, associated active salpingitis ..	3	1	Two repeat biopsies showed occasional plasma cells. No plasma cells one year after original biopsy.
Normal late premenstrual endometrium	1	—	—
Chronic endometritis, associated active salpingitis	1	—	—
Moderate Numbers of Plasma Cells			
Total number of cases .. 10			
Normal premenstrual endometrium	5	2	Both cases showed small numbers of plasma cells up to one year after original section.
Non-premenstrual endometrium, associated active salpingitis ..	5	4	Two showed no plasma cells up to one year after original section. One showed occasional plasma cells up to one year after original section. One became pregnant within a year of original section.
Small Numbers of Plasma Cells			
Total number of cases .. 31			
Normal premenstrual endometrium, no associated salpingitis	27	11	Eight showed no plasma cells up to one year after original section. One had hysterectomy for menorrhagia 4 months after the original section. No plasma cells in endometrial section. Two became pregnant within a year of original section.
Non-premenstrual endometrium, chronic cervicitis	4	2	One showed no plasma cells in repeat premenstrual biopsies up to one year after the original section. One had hysterectomy for menorrhagia 4 months after original section. The endometrium showed occasional plasma cells. The cervix showed the changes of chronic cervicitis.

lymphocytes and macrophages. The stromal cells themselves appeared smaller and less prominent than normal. There was no increase in collagen or reticulum content of the endometrium as a whole. The case was associated with an active sub-acute salpingitis. The remaining 4 were apparently normal premenstrual endometria (i.e., within 7 days of expected menstruation and showing glandular secretory activity) with no other deviation from the normal apart from the presence of the plasma cells. In 3 of the 4 there was an associated active chronic salpingitis whilst in the remaining 1 taken within 24 hours of the expected onset of menstruation there was no associated inflammatory lesion of the tubes, parametrium or cervix.

It was only found possible to repeat the examination of the endometrium in 1 of the 5 cases. In this patient 2 repeat biopsies showed a few plasma cells in the premenstrual endometrium but one year after the original curettage no plasma cells were present in the premenstrual endometrium and the histological picture continued to be normal in every respect. The

salpingitis had by this time completely settled clinically. One further case in which active chronic salpingitis was present was seen again a year later with persistent symptoms attributable to the salpingitis and, following laparotomy, this diagnosis was confirmed. The patient with true chronic endometritis was a mental defective and it was not possible to persuade her to attend the follow-up clinic.

Moderate Numbers of Plasma Cells in the Endometrium

In this category there were 10 cases, and apart from the plasma cells no other histological abnormality was demonstrable in the endometrium. Five were premenstrual and 5 were not. The latter were in every case associated with clinically active chronic salpingitis.

Two of the cases of normal premenstrual endometrium not associated with chronic salpingitis were followed up and both showed occasional plasma cells in one or more repeat premenstrual biopsies up to one year after the original section. Of the 4 cases associated with chronic salpingitis which were followed up 2 showed no plasma cells in one or more repeat premenstrual biopsies up to one year after the original section, whilst one patient became pregnant after a course of treatment for chronic salpingitis. No plasma cells were present in a premenstrual endometrial biopsy taken from this patient 5 months after delivery.

Small Numbers of Plasma Cells in the Endometrium

In these cases only occasional plasma cells were found in the section stained with Pyronine and Methyl-Green. Thirty-one such cases were found of which 27 were normal premenstrual endometrium showing no abnormality apart from the plasma cells. The remaining 4 were not premenstrual but showed non-secretory endometrium with small numbers of plasma cells. Each one of these 4 cases was associated clinically with a chronic cervicitis, but there was no evidence of inflammatory lesions elsewhere in the genital tract.

Thirteen of these cases were followed up and only 1 showed a small number of plasma cells in the endometrium subsequently. In this case a hysterectomy was performed 4 months after the original section. The endometrium was quite normal and the only abnormality found histologically was a chronic cervicitis. There was no evidence of chronic salpingitis. Two of the patients became pregnant within a few months of the original section.

Discussion

In every one of the 27 cases in which *small numbers of plasma cells were found in the premenstrual endometrium* no other histological abnormality was found, and clinically there was no association with inflammation in any other part of the genital tract. The cases which were followed up did not show plasma cells in subsequent biopsies, which suggests that the finding is irregular and inconstant, and is a point against drawing any conclusion from their presence in the original section. Two cases became pregnant within a short time of the biopsy being taken, so there would seem to be no reason to suppose that the presence of small numbers of plasma cells in the premenstrual endometrium is a bar to conception and successful pregnancy.

None of the 4 non-premenstrual cases showing small numbers of plasma cells had any evidence of chronic salpingitis but all had a chronic cervicitis. The significance of this finding is uncertain but it has been observed clinically (Peel, 1954) that patients suffering from menorrhagia who have a chronic cervicitis experience symptomatic relief from the menorrhagia after successful treatment of the cervicitis.

It would seem from a consideration of the results obtained that small numbers of plasma cells in the premenstrual endometrium are of no significance and do not suggest the presence of inflammatory processes elsewhere in the genital tract. Such a conclusion agrees with histological findings elsewhere in the body. No significance would be attached to the finding of a few isolated plasma cells in other sites, and it would seem unreasonable to do so in the case of the endometrium, especially at a time when it is being subjected to an avascular necrosing process.

Cases showing *more than a few plasma cells but still falling short of a heavy infiltration of the endometrium* may also be simply the result of normal, late premenstrual changes. Five of the 10 cases in this category showed otherwise

normal premenstrual endometrium and there was no associated inflammatory lesion elsewhere. Two of these patients when followed up over a period of a year continued to show occasional plasma cells in the premenstrual endometrium without any other histological or clinical abnormality being present. All 5 cases in which a moderate number of plasma cells were found in a non-premenstrual endometrium were associated clinically with chronic salpingitis in varying degrees of activity. Of 4 of these cases followed up only 2 showed a few plasma cells in subsequent premenstrual biopsies, and one showed none at all. One patient became pregnant within a few months of the original section. These results suggest that the finding of more than a few plasma cells in the endometrium (apart from the late premenstrual stage, when it may be a part of the normal menstrual phenomenon), raises the possibility of chronic inflammatory lesions in the tubes, to which attention should accordingly be directed.

Five specimens in the series showed *a heavy infiltration of the endometrium by plasma cells* and on this basis could be diagnosed by the criterion of Hitschmann and Adler as chronic endometritis. Careful histological examination, however, revealed that in only 1 case was there sufficient additional round cell and polymorphonuclear infiltration of the stroma to warrant such a diagnosis. This patient had an active subacute salpingitis at the time the specimen was obtained. In the remaining 4 sections the endometrium (which was premenstrual in every case) appeared to be quite normal apart from the presence of the plasma cells, and there was no marked round cell or polymorphonuclear infiltration. Of these 4 cases 3 had an associated salpingitis, whilst the remaining 1 was taken from a nulliparous patient without any evidence of a pelvic inflammatory lesion but within 24 hours of the expected onset of menstruation. From these results it is deduced that, apart from true chronic endometritis, a heavy infiltration of the endometrium by plasma cells may occur in association with active chronic salpingitis especially premenstrually or occasionally in the premenstrual endometrium within a very short time of the onset of menstruation.

Thus in the present series only 1 true case of chronic endometritis was discovered, an incidence of less than 0·2 per cent. Because this figure seemed to be at variance with the reported incidence of chronic endometritis, a search was made through the records of the Department of Pathology for the past 7 years. Four further cases diagnosed histologically as chronic endometritis were discovered and fresh sections were cut and stained by the Pyronine-Methyl-Green technique and also with haemotoxylin and eosin. Three of these showed considerable polymorphonuclear and round cell infiltration of the endometrium as well as large numbers of plasma cells, and all 3 cases were associated clinically with chronic salpingitis. The remaining case showed normal premenstrual endometrium apart from the presence of large numbers of plasma cells; this section was obtained from a patient who was within 24 hours of the expected onset of menstruation and there was no evidence of an associated chronic salpingitis. In this case it was not considered that the diagnosis of chronic endometritis could be substantiated.

One case of chronic endometritis associated with chronic salpingitis which was followed up showed occasional plasma cells in a normal premenstrual endometrium obtained in 2 subsequent premenstrual biopsies at 3-monthly intervals, but a year after the original section was obtained no plasma cells were present in the premenstrual endometrium and clinical evidence of active chronic salpingitis was no longer obtainable. This case would seem to conform to the observation of Schröder and Neuendorff-Viek (1921) that adnexitis in the quiescent stages is not associated with plasma cells in the endometrium. In 1 of the cases in which the diagnosis of chronic endometritis was made laparotomy was performed at the time at which the initial endometrial biopsy was obtained; biopsy of one of the tubes confirmed the existence of a chronic salpingitis although one year later, when a hysterectomy was performed, the tubes had returned to normal and the endometrium showed only occasional plasma cells. One case had a laparotomy 3½ years after the original biopsy because of continued symptoms ascribed clinically to an active chronic salpingitis and at laparotomy this diagnosis was confirmed.

The picture seen in these 4 additional cases of heavy infiltration of the endometrium by plasma

cells conforms to the pattern of the findings in the main series and confirms the rarity of true chronic endometritis as opposed to those cases which merely show an infiltration of the endometrium by plasma cells. In every case diagnosed as chronic endometritis an associated tubal lesion was found although cases of isolated chronic endometritis have been described by Dumoulin and Hughesdon (1951). It seems unlikely on general grounds that persistent chronic endometritis can occur in the absence of active tubal infection and this is confirmed by the results of the present series.

The discrepancy between the incidence of chronic endometritis in this series and in other reported series (11 per cent Sutherland, 1949; 6 per cent Woden and Cordier, 1947; 30·7 per cent Buttner, 1910), may be explained on the following grounds:

1. Particular care has been taken to exclude all cases associated with recent abortion (i.e., within 3 months) or full-time delivery, as well as cases of tuberculosis, malignant disease, polypi and metropathia haemorrhagia. These lesions show a variable degree of plasma cell infiltration which may or may not be associated with other evidence of chronic inflammation.

Post-menopausal endometritis has also been excluded as being a separate entity.

2. The presence of plasma cells *per se* has not been taken to be sufficient evidence of chronic endometritis, but other evidence, particularly extensive polymorphonuclear and round cell infiltration sometimes associated with early proliferative changes in the stroma, was deemed essential for the diagnosis.

3. As a corollary to 2 it was recognized that plasma cell infiltration, even sometimes heavy plasma cell infiltration, may occur in normal premenstrual endometrium in cases associated with active tubal inflammation or less commonly in normal premenstrual endometrium immediately prior to menstruation.

Conclusions

Plasma cell infiltration of the endometrium of slight or moderate degree is a fairly common occurrence and is usually a transitory phenomenon to which no significance should be attached.

Plasma cell infiltration of the endometrium is not of itself sufficient evidence on which to base a diagnosis of chronic endometritis, which is a rare condition. (An incidence of 0·2 per cent in the present series.)

Heavy plasma cell infiltration is almost invariably associated with active salpingitis.

Summary

An attempt has been made to investigate the occurrence of plasma cell infiltration of the endometrium and its relation to chronic endometritis. Specimens from 608 patients were examined microscopically using a special staining technique to demonstrate plasma cells.

The results obtained are analyzed and their significance discussed.

I am deeply indebted to Professor H. A. Magnus for his help in interpreting some of the sections and to Mr. J. H. Peel and Mr. S. G. Clayton for their advice and assistance. Preparation and staining of the specimens was carried out by Mr. S. Hardy.

This work was made possible by a grant from the King's College Hospital and Medical School Research Committee.

References

Buttner, O. (1910): *Arch. Gynäk.*, **92**, 781.
Dumoulin, J. G., and Hughesdon, P. E. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 222.
Hitschmann, N. F., and Adler, L. (1907): *Z. Geburtsh. Gynäk.*, **60**, 63.
Keene, P. E., and Payne, F. L. (1934): *Sth. med. J.*, **27**, 108.
Magnus, H. A. (1954): Personal communication.
Markee, J. E. (1940): *Contr. Embryol. Carneg. Instn*, **28**, 223 (No. 177).
Pappenheim, A. (1899): *Arch. path. Anat.*, **157**, 19.
Peel, J. H. (1954): Personal communication.
Rosa, C. G. (1950): *Stain Tech.*, **25**, 165.
Schiller, W. (1948): *in* Anderson, W. A. D., *Pathology*. London: Kimpton. p. 1149.
Schröder, R., and Neuendorff-Viek, F. (1921): *Arch. Gynäk.*, **115**, 15.
Sutherland, A. M. (1943): *J. Obstet. Gynaec. Brit. Emp.*, **50**, 161.
Sutherland, A. M. (1949): *Glasg. med. J.*, **30**, 303.
Trevan, D. J., and Sharrock, A. (1951): *J. Path. Bact.*, **63**, 326.
Woden, J. L., and Cordier, R. (1947): *Rev. franç. Gynéc.*, **42**, 161.

PREMATURE BABIES IN THE TROPICS

BY

DEREK LLEWELLYN-JONES, M.B., M.A.O.

Obstetrician

General Hospital, Kuala Lumpur

IN 1920, Ylppö proposed that the critical weight below which an infant should be classed as premature was 2,500 g. or 5 pounds 8 ounces. Later, in 1937 this standard was accepted and adopted by an international committee. According to this definition, any infant weighing 2,500 g. or less at birth is regarded as premature, regardless of the period of the gestation.

Whilst this standard is applicable to the northern countries of Europe and America it is of little value when dealing with babies born in other parts of the world. The average birth weight of white Americans is 7·56 pounds (Bivings, 1934) and of English babies 7·46 pounds (McKeown and Gibson, 1951). But in many lands the average birth weight of singleton births considered to be full term is far less. The Bantu in South Africa have an average birth weight of 6·8 pounds (Salber and Bradshaw, 1951), the Sinhalese of 6·15 pounds (Collumbine, 1950) and the Singapore Chinese of 6·8 pounds (Millis, 1953).

Now the incidence of prematurity in England and the United States of America is considered to lie between 5 and 10 per cent (Crosse, 1945 and Greenhill, 1946–51). If the accepted standard of prematurity is applied to infants born in tropical lands a very much higher percentage will be classed as premature by this standard. Thus in Southern Rhodesia, Houghton and Ross (1953) find that 16·6 of African babies are premature.

It was therefore considered worthwhile to determine the average birth weight of babies born in the Maternity Unit of the General Hospital, Kuala Lumpur, to assess the incidence of prematurity and to see whether any other standard could be adopted.

THE MATERNITY UNIT

The Maternity Unit has 100 beds, divided into an antenatal ward of 30 beds and two postnatal wards of 35 beds each. The hospital takes all the abnormal obstetrics from a population of over 500,000 and as well as this no normal patient seeking delivery is refused admission. The proportion of admissions varies between the races. In 1953, 46 per cent were South Indian, 44 per cent Chinese, 6 per cent Malay and 4 per cent Pakistanis. The South Indians are drawn from the poorer classes working on rubber estates or as labourers, the Chinese from the poorer and middle classes usually living in Kuala Lumpur or the surrounding New Villages. In consequence of this, and of racial habits, the diet of the two races varies, the Chinese receiving the better diet. Toxaemia of pregnancy is more common amongst the Chinese, anaemia amongst the South Indians.

During 1953, 4,229 women were delivered whose babies weighed 2 pounds or more at birth. Only these babies have been considered in this report.

Since few of the women knew the period of their gestation and since the physical signs of maturity are difficult to determine with accuracy it has not been possible to include only "full-time singleton" births in order to find the average birth weight. Two calculations have been made. The first includes all births of 2 pounds or more; the second excludes all births of 4 pounds 7 ounces and below. The average "full-time singleton birth weight" should lie somewhere between these two figures. For comparison the figures of all deliveries classed as normal occurring between June, 1951 and December, 1953 are given.

TABLE I

Average birth weights of infants born in Kuala Lumpur, Malaya

Date	Race	All births		Infants below 4·5 pounds excluded	
		Number	Average birth weight	Number	Average birth weight
1953	South Indians	1,931	5 pounds 12¾ ounces	1,707	6 pounds 2 ounces
1951–2	South Indians	2,765	5 pounds 13½ ounces	2,476	6 pounds 1 ounce
1953	Chinese	1,897	6 pounds 6·9 ounces	1,770	6 pounds 10·2 ounces
1951–2	Chinese	2,108	6 pounds 4½ ounces	1,994	6 pounds 6·7 ounces
1951–2	Malay	322	6 pounds 0·8 ounces		

In view of the few Malay women delivered it was felt that any conclusions drawn from the birth weight of their infants would be invalid and so, except in the next paragraph and when considering the work of the premature baby unit, they have been ignored.

If Ylppö's standard of prematurity is accepted, during 1953, 35·1 per cent of South Indian babies were premature, 16·6 per cent of Chinese babies were premature, 22·5 per cent of Malay babies and 23·5 per cent of Pakistani babies were premature.

Since most of these "premature" infants were vigorous at birth, looked well, sucked well and progressed well it is clear that they cannot all be considered premature.

It was therefore decided to adopt a lower standard of prematurity. By tradition my predecessors had classed all babies below the weight of 4·5 pounds as premature and it was determined to see if this weight was acceptable.

THE PREMATURE BABY UNIT

In 1953, a total of 288 babies were born alive whose birth weight was below 4·5 pounds. In addition there were 101 stillbirths.

On my arrival in January there was no premature baby unit but it was possible to start a 12-bedded unit in early February. The unit is under the charge of a staff nurse, who also has other duties, and is helped by two or more midwives if they can be spared. Because of the great staff shortage a very simple regime has had to be adopted.

The babies are nursed in "Sorrento" cots. Luckily the climate of Malaya is favourable to premature babies. The average day temperature is 89 degrees Fahrenheit, and at night the temperature falls to 73 degrees Fahrenheit but rarely lower. The humidity is always high.

Treatment is simple. The babies are seen daily by me but the general care of the unit is by the staff nurse. If an infant is cyanosed at birth or has cyanotic attacks it is nursed in an oxygen tent for 24 to 48 hours but rarely longer. Intragastric oxygen has not been used so far. Babies showing no cyanosis are nursed in their cots without additional oxygen. Feeding is by breast or bottle if the baby is strong enough to suck, and by tube, pipette or spoon if not. Feeds are given 3-hourly starting 24 hours after birth. If an infant fails to gain in weight in spite of adequate intake it is given oral penicillin. Concentrated vitamin A and D (BPC) is given from the 7th day and mist. ferri et ammon. cit. pro infant is started about the same time. When possible breast milk is used to feed the infants, but often spray-dried milk has to be used.

In order to keep the work of the unit at a minimum, although all babies of 4·5 pounds and under are admitted at birth, those whose weight exceeds 4·25 pounds and who are vigorous are sent to the postnatal wards to be nursed with their mothers. Should they deteriorate later they are readmitted to a section of the premature baby unit.

Of the 288 babies admitted to the unit during the year, 191 were discharged alive. This is 66·3 per cent of all admissions whose birth weight lay between 2 pounds and 4·5 pounds. Table II shows the results of all babies who were delivered during 1953.

It can be seen from the Table that there is a steep drop in neonatal mortality and in total

TABLE II
All Babies

Weight Pounds and Ounces	Live	Neo. death	SB.	Total	Percentage Mortality	Percentage Mortality (excluding stillbirths)
2 0—2 7	1	10	26	37	97·3	90·9
2 8—2 15	4	20	16	40	90·0	83·3
3 0—3 7	20	25	28	73	72·6	55·5
3 8—3 15	43	11	14	68	36·7	20·4
4 0—4 7	123	31	17	171	28·0	21·3
4 8—4 15	212	10	7	229	7·4	4·5
5 0—5 7	405	9	28	442	8·2	2·2
5 8—5 15	578	9	10	597	3·2	1·5
6 0—6 7	810	8	13	831	2·5	1·0
6 8—6 15	733	2	13	748	2·0	0·25
7 0—7 7	518	5	4	527	1·7	1·5
7 8—7 15	285	2	0	287	0·7	0·7
8 0—8 7	149	1	5	155	3·9	0·66
8 8—8 15	47	0	3	50	6·0	0·0
9 0+	28	0	4	32	12·5	0·0

TABLE III
South Indian Babies

Weight Pounds and Ounces	Live	Neo. death	SB.	Total	Percentage Mortality	Percentage Mortality (excluding stillbirths)
2 0—2 7	1	7	13	21	95·2	87·5
2 8—2 15	3	12	10	25	88·0	80·0
3 0—3 7	11	11	19	41	73·2	50·0
3 8—3 15	27	7	9	43	37·2	20·6
4 0—4 7	79	10	5	94	15·9	11·2
4 8—4 15	142	2	6	150	5·3	1·3
5 0—5 7	254	6	10	270	6·0	2·3
5 8—5 15	307	4	6	317	3·1	1·2
6 0—6 7	374	5	8	387	3·3	1·0
6 8—6 15	265	1	9	275	3·6	0·4
7 0—7 7	183	1	2	186	1·6	0·5
7 8—7 15	70	0	0	70	0	0
8 0—8 7	39	0	1	40	2·5	0
8 8—8 15	5	0	0	5	0	0
9 0+	6	0	1	7	0	0

mortality when the birth weight of 4 pounds 7 ounces is exceeded. If this is granted and it is accepted that 4 pounds 7 ounces (and this is approximately 1,999 g.) is the upper limit of prematurity what percentage of deliveries in the hospital are premature?

Including stillbirths, 389 babies were born whose birth weight was less than 4·5 pounds. This is 9·08 per cent of all deliveries. If the 101 stillbirths are excluded 288 infants remain, or 6·72 per cent of all deliveries. This percentage is similar to that found in Great Britain and the U.S.A.

These mortality rates are overall figures for all races. South Indian babies and Chinese babies are considered separately in Tables III and IV.

From these Tables it can be seen that whilst the steep drop in mortality still occurs at 4·5

TABLE IV

Chinese Babies

Weight Pounds and Ounces	Live	Neo. death	SB.	Total	Percentage Mortality	Percentage Mortality (excluding stillbirths)
2 0—2 7	0	3	11	14	100	100
2 8—2 15	1	5	5	11	90·9	83·3
3 0—3 7	6	12	6	24	75·0	66·6
3 8—3 15	10	4	3	17	41·2	28·8
4 0—4 7	35	18	8	61	42·6	33·9
4 8—4 15	41	5	1	47	12·7	10·8
5 0—5 7	116	3	11	130	10·7	2·5
5 8—5 15	212	3	3	218	2·8	1·4
6 0—6 7	358	1	4	363	1·1	0·3
6 8—6 15	383	1	3	387	0·8	0·3
7 0—7 7	275	4	1	280	2·8	1·4
7 8—7 15	180	2	0	182	1·1	1·1
8 0—8 7	101	1	3	105	3·8	1·0
8 8—8 15	41	0	3	44	6·5	0
9 0+	12	0	2	14	14·2	0

TABLE V

All Babies remaining in Hospital for Five Days or Dying in that Time

Weight Pounds and Ounces	Live	Neonatal death	Total	Percentage Mortality
2 0—2 7	2	12	14	85·7
2 8—2 15	4	17	21	81·0
3 0—3 7	18	22	40	55·0
3 8—3 15	37	11	48	23·3
4 0—4 7	117	25	142	17·6
4 8—4 15	122	6	128	3·0
5 0—5 7	177	8	185	4·3
5 8—5 15	214	7	221	3·2
6 0—6 7	244	6	250	2·4
6 8—6 15	200	2	202	1·0
7 0—7 15	100	6	106	5·6
8 0—8 15	42	1	43	2·3
9 0+	6	0	6	—

pounds in the case of the South Indians, in the case of the Chinese the drop is less steep and extends into the 4 pounds 8 ounces to 5 pounds group. It is possible therefore that Chinese babies below the weight of 5 pounds should be considered premature. Against this is the difficulty of applying two standards and the fact that the majority of the premature babies are Indian. This coupled with the clinical observation that most of the Chinese babies of 4·5 pounds and over are vigorous leads me to retain the lower level of prematurity as the one to be adopted in this hospital.

Because of the shortage of beds, primiparae stay in hospital for 5 days or more but multigravidae are discharged after 48 to 72 hours if no contra-indication exists. It could be argued that the rates in Table II are favourably weighted towards the lower birth weights as some of the heavier babies will certainly die at home. Table V shows the mortality rates for all babies who remained in the hospital for more than 5 days.

It can be seen that the same fall in mortality occurs at the 4·5 pounds level.

Discussion

Two facts became clear during the course of this investigation. Firstly that the international standard of prematurity confused rather than clarified the issue when applied to babies born in tropical lands. If that standard was used abnormally favourable mortality rates would be shown and the percentage of premature babies would be abnormally high. Each country and each race will have to decide upon its own standard of prematurity but as far as possible this should be made so that comparisons can be effected between it and other lands. To this end if a premature rate of between 5 and 10 per cent of all deliveries is aimed at, and if this rate is confirmed by mortality tables, figures which are comparable will be obtained.

The second matter is more conjectural. It is this. How far are we justified in expending money for vast and complicated premature baby units? The experience so far in Kuala Lumpur has shown that results comparable with those of the better units in America and the British Isles can be obtained with the minimum of equipment and staff. The mothers of these babies are all undernourished and anaemic by European standards and yet their babies survive. Is this a racial tenacity or what is it? The treatment is of the simplest order; but the staff is devoted, and although the pupil midwives are constantly changing, their work is good. Because they are constantly changing the routine has to be simple. Crosse (1945) recommends 2 nurses to every 3 babies; in this unit we are lucky if we have 2 nurses to every 6 babies.

But we do have a favourable climate. Both the temperature and the relative humidity are ones in which premature babies do well.

Could it not be that these are the major factors in the survival of premature infants? If a ward can be conditioned to a temperature of between 75 and 85 degrees Fahrenheit and a relative humidity of 70 per cent or more, and, if a devoted nurse can be found to look after the infants, more may not be necessary. In this unit we do not believe in excessive oxygenation of the infants or in the administration of hormones. We do believe that care should be taken to prevent cross infection, that regular feeding is essential (we have found 3-hourly feeding successful even in the smallest infants) and that the babies should be disturbed as little as possible. We would like breast milk to be available for all, but we have not been able to organize this so far and our impression is that there is little difference between breast and dried milk in premature baby feeding. But this is only an impression and we cannot subject it to statistical analysis. Over the next year or two we hope to find out more about this.

Summary

The results of a year's work in a premature baby unit are described. It is considered that a new standard of prematurity will have to be found for tropical lands.

It is suggested that this standard should be 4 pounds 7 ounces (approximately 1,999 g.) but that each country should investigate its own people.

My thanks are due to the medical and nursing staff of the Maternity Department, General Hospital, Kuala Lumpur, without whose care these results could not have been obtained. My thanks are also due to the Director of Medical Services, Federation of Malaya for permission to publish.

References

Bivings, L. (1934): *Amer. J. Obstet. Gynec.*, **27**, 725.
Collumbine, H. (1950): *Ceylon J. med. Sci.*, **7**, 19.
Crosse, V. M. (1945): *The premature baby.* London: Churchill. p. 120.
Greenhill, J. P. (1946–1951): *Yearb. Obstet. Gynec.*, Chicago.
Houghton, J. W., and Ross, W. F. (1953): *Trans. R. Soc. trop. Med. Hyg.*, **47**, 62.
McKeown, T., and Gibson, G. R. (1951): *Brit. J. soc. Med.*, **5**, 98.
Millis, J. (1953): *Med. J. Malaya*, **7**, 168.
Salber, E. J., and Bradshaw, E. S. (1951): *Brit. J. soc. Med.*, **5**, 113.
Ylppö, A. (1920): *Z. Kinderheilk.*, **24**, 1.

FIBRINOGENAEMIA IN AN ISO-SENSITIZED MOTHER CARRYING A DEAD FOETUS

BY

LOUIS J. QUINN, B.A., M.D., M.R.C.O.G., F.R.C.S.(C.)
Associate Obstetrician and Gynaecologist

AND

J. A. HARPER, M.D.
Resident in Obstetrics and Gynaecology
St. Mary's Hospital, Montreal, Canada

THE prophylaxis, prompt recognition and early institution of proper therapy in the condition of hypofibrinogenaemia complicating pregnancy will prevent obstetrical deaths from uncontrollable haemorrhage.

Great advances have been made in the treatment of the altered blood coagulability consequent to pregnancy since it was first recognized as temporary haemophilia by De Lee in 1901. The state of hypofibrinogenaemia during pregnancy was first demonstrated by Dieckmann in 1936, who found reduced levels of blood fibrinogen in patients with haemorrhage following abruptio placentae.

The fact that fibrinogen depletion or hypofibrinogenaemia does occur in abruptio placentae is well established. In this condition the mechanism whereby this clotting defect is brought about revolves about the fibrinolysin theory championed by Weiner, Reid, Roby and Diamond (1950) and the thromboplastin or fibrin embolism theory of Schneider (1951a).

Less well recognized is the fact that the prolonged retention of the dead foetus will result in a deficiency in circulatory fibrinogen which can prove to be as disastrous as the similar disorder in the more common abruptio placentae.

Abruptio placentae can develop even after long standing foetal death as pointed out by Schneider (1951b). However, in cases such as the one described below in which there is no evidence of abruptio placentae, either recent or old, it must be assumed that the incoagulability of the maternal blood is the result of the retention of the dead foetus.

CASE REPORT

The patient was a 24-year-old white woman, para-2, gravida-3, now pregnant for the third time. Her first pregnancy was quite uneventful. She experienced a normal antenatal course. The Rh factor was checked at 3½ months and she was reported group O Rh negative; her husband group O Rh positive. Five weeks before delivery she was checked again and no antibodies were present. Labour was about 19 hours and was terminated by low forceps under spinal anaesthesia, with the aid of median episiotomy. The blood loss was 300 ml. The baby, a girl, weighing 6 pounds, 9 ounces, cried spontaneously on being born and exhibited no signs of erythroblastosis. The baby was group O Rh positive.

The patient became pregnant for the second time 10 months later. Again the antenatal course was normal, and 5 weeks before term no antibodies were present. She went into labour 3 weeks before her expected date. Labour was 8 hours but the foetal heart became quite slow after about 7½ hours of labour and, though the patient was given nasal oxygen, the foetal heart disappeared before delivery could be effected. The foetus was deadborn and covered with meconium—a girl, weighing 5 pounds, 8 ounces, with two very tight coils of cord about the neck and a true knot in cord. The baby showed no maceration of skin and exhibited signs of erythroblastosis by an enlarged liver and spleen. The placenta was very thick and spongy and weighed 2 pounds, 3 ounces. The blood loss was about 300 ml. The post-partum course was normal. Cord blood showed the foetus to be group O Rh negative.

The present pregnancy (3rd) started about 8 months after delivery of her second baby. At about 6 months she was reported as having blocking antibodies, anti D1:4. the husband genotype was CDE/cde and the fact that he was heterozygous was confirmed by the negative Rh

factor of the second child. Life was felt by the mother at about the eighteenth week and continued until the twenty-fourth week, when she reported the baby had ceased moving and on examination the foetal heart could no longer be heard. The patient was allowed to go into labour spontaneously which she did approximately 9 weeks after disappearance of the foetal heart. Labour was only 4½ hours and she delivered spontaneously a dead, badly macerated male foetus; no episiotomy was required and there was a minimum trilene anaesthesia. The placenta came away within a few minutes, was small, and there was no evidence of retroplacental haemorrhage, but about 200 ml. of bright fresh liquid blood came with the placenta. The patient was given 0·2 mg. ergometrine I.V. following delivery of the placenta, but very brisk bleeding continued from the uterus. The cervix was inspected for lacerations but none were found and, as bleeding continued, the uterus was explored with the hand; no lacerations were found but a few pieces of old membranes were removed. Ergometrine, 0·2 mg., was repeated and, as bleeding still persisted, a transfusion of emergency Rh negative blood was started. At this time blood was taken from the patient to determine her clotting ability and it was discovered that her blood did not clot after one-half hour and there also were no clots found in the vagina from the bleeding. Accordingly it was at once realized that we were dealing with a case of defective clotting mechanism. The blood bank was contacted and more blood obtained and continuous transfusions kept running as she was still bleeding and only by keeping blood running could the blood pressure and pulse be maintained at satisfactory levels.

Some fibrinogen was obtained from another hospital which had the only supply available in the city. The patient had been given 2,500 ml. of blood and still her blood did not clot, so 2 g. of fibrinogen was administered I.V., and blood taken one-half hour later clotted in 3½ minutes. The bleeding per vaginam had stopped and some well formed clots were obtained for the first time from the vagina.

From this point on, there was no further bleeding and no more fibrinogen had to be given. The post-partum course was uneventful and the patient made an excellent recovery. She was discharged on the ninth day; haemoglobin 12·4 g., haematocrit 36 per cent, prothrombin time 15 seconds, control 15 seconds, bleeding time 2 minutes, clotting time 5 minutes, clot retraction good, platelet count normal.

Blood taken from the patient before the administration of the fibrinogen showed no fibrinogen present, whereas a sample, taken after the fibrinogen was given, showed the lowest normal level of fibrinogen to produce clotting.

As pointed out by Hodgkinson, Margulis and Luzarde (1954) in their most lucid paper on the subject, the sequence of events leading to fibrinogen depletion in an Rh iso-sensitized patient after prolonged retention of a deadborn infant is not clear cut. These authors point out that absorption of intra-uterine material into the maternal circulation is necessary for the disappearance of maternal circulating fibrinogen. In the absence of abruptio placentae, transgression of the decidual barrier could occur through absorption of intraovular fluid after autolytic degeneration of the placenta and membranes. This mechanism has been postulated for amniotic fluid embolism.

As mentioned in the present case report and as reported by others, fibrinolysis is a prominent feature in hypofibrinogenaemia occurring in Rh-iso-sensitized patients. Stefanini and his colleagues (1953) have recently described an antibody type of coagulation defect occurring in pregnant women near term, especially when there is Rh incompatability between mother and child. In many cases of abruptio placentae the lysis of the formed clot does not occur. However, in cases of hypofibrinogenaemia due to retention of a dead baby, the lysis of the clot, if formed, may readily occur, if presumably due to a fibrinolysin. In normal pregnancy following delivery, however, there may be increased fibrinolysis.

Management of the Pregnancy Complicated by Death of the Foetus in an Rh-iso-sensitized Mother

Early recognition of the death *in utero* is, of course, of utmost importance. This is especially important in the Rh iso-sensitized mother and the routine Rh typing and antibody determinations are essential. A rising titre should be watched with suspicion. The actual discovery of death *in utero* from other conditions need not be mentioned.

If death *in utero* is discovered the detection of fibrinolysis in her blood may be possible long before delivery or before the development of any haemorrhagic complication. This may be done by performance of the simple test outlined by Weiner *et al.* (1950). Blood is allowed to clot in a glass test tube at 37 degrees C and is observed for 24 hours. If the clot dissolves, fibrinolysis is present. Blood fibrinogen levels should then be determined as well as the other standard tests used in blood clotting derangements, the most important of which is the clotting time, which is prolonged in this condition.

When death of the foetus is found to be present, with a known coagulation defect a conservative course is usually the safest one to follow. Patients with a major coagulation defect do not withstand an operation well. The value of a priming dose of oestrogens or other hormonal preparations is equivocal. Reid states that stimulation with pituitary substances is contraindicated because of the possibility of issuing more toxic substances from the placenta into the maternal circulation. Rupture of the membranes, if possible, is of value.

As in the case with abruptio placentae, the first manifestation of a defect in the blood clotting mechanism may be the onset of excessive post-partum bleeding. If this proves to be the case, one should realize where the coagulation defect lies. If hypofibrinogenaemia is present, it may be detected by three simple tests, namely, (1) the clotting time and clot retraction behaviour, (2) the presence of fibrinolysin, (3) fibrinogen levels.

In those patients with hypofibrinogenaemia who are bleeding actively, experience has shown that it is impossible to administer citrated blood at a sufficient rate to increase the blood fibrinogen concentration to an effective coagulant level. Although the fibrinogen content of banked blood remains stable there is some evidence that the prothrombin activity and platelet content become decreased. In this respect the use of fresh whole blood would serve a more suitable purpose.

The treatment of choice is the administration of adequate amounts of fibrinogen. This immediately corrects the defect responsible. Blood replacement therapy is indicated only to replace the lost volume and should in no way be considered as an aid in correcting the underlying defect. It is to be hoped that in those cases of excessive bleeding due to hypofibrinogenaemia, the days of giving multiple transfusions of citrated blood and then condemning the patient to the so-called heroic hysterectomy, should now be passed.

In passing it may be noted that good results have been recently reported with cortisone therapy in the treatment of hypofibrinogenaemia by Stefanini and Gendel. This may prove to be of value in the prophylactic treatment of this condition.

Summary

The diagnosis and treatment of hypofibrinogenaemia resulting from prolonged retention of a dead foetus has been outlined. An illustrative case report has been given. Early diagnosis of hypofibrinogenaemia by means of clotting and clot retraction time, the presence of fibrinolysins and the fibrinogen levels in the blood are standard aids in the diagnosis. Replacement with fibrinogen is the treatment of choice.

References

Dieckmann, W. J. (1936): *Amer. J. Obstet. Gynec.*, **31**, 734.

Hodgkinson, C. P., Margulis, R. R., and Luzarde, J. H. (1954): *J. Amer. med. Ass.*, **154**, 557.

Schneider, C. L. (1951a): *Surg. Gynec. Obstet.*, **92**, 27.

Schneider, C. L. (1951b): *Bull. Margaret Hague Hosp.*, **4**, 2.

Stefanini, M., Campbell, E. W., Plitman, G. I., and Salomon, L. (1953): *Bull. New Engl. med. Cent.*, **15**, 23.

Weiner, A. E., Reid, D. E., Roby, C. C., and Diamond, L. K. (1950): *Amer. J. Obstet. Gynec.*, **60**, 1015.

CAESAREAN SECTION IN ECLAMPSIA

BY

DR. M. K. KRISHNA MENON, B.A., M.D.

Professor of Clinical Obstetrics and Gynaecology
Madras Medical College

Obstetrician and Gynaecologist
Government Hospital for Women and Children, Egmore, Madras, India

IN spite of concentrated, continuous and large scale investigations, the aetiology of eclampsia still remains obscure. And therefore at best the curative treatment of eclampsia can only be symptomatic and empirical.

There was the era from 1745–1846 when the main treatment was purging, sweating and bleeding. 1847–1895 saw the addition to it of manual dilatation of the cervix and forcible delivery. 1896–1905 was the era of immediate delivery by accouchment force or vaginal hysterotomy. During 1906–1918 we see the practice of immediate delivery by abdominal Caesarean section or vaginal hysterotomy. Also we see at this stage the development of the two well-known lines of treatment—the elimination treatment as advocated by Tweedy of Rotunda and the sedative treatment as advocated by Stroganoff in Russia. During 1918–1927 we see the addition of intravenous injections of hypertonic glucose solution and magnesium sulphate. To his method in 1928 Stroganoff added the induction of labour by artificial rupture of membranes. All through these years, obstetricians have recognized sedation and elimination as the main principles in the treatment. And it is in the techniques employed to gain these ends that the various methods differed. There is no doubt that the sedative line of treatment—the so-called conservative treatment of eclampsia—has come to stay. There is also no doubt that the method perfected by Stroganoff and altered by various clinics to suit their own particular needs has considerably reduced the maternal mortality from eclampsia. But have we achieved the irreducible minimum? Can we by any other method or a combination of methods reduce the mortality further? It is from this angle that I approach the problem.

Every one realizes the importance of efficient antenatal care in the prevention of eclampsia. We, here, are however in the unfortunate position of having to deal with a very large number of eclamptics. I remember the days of 1933–1935 when we used to treat these patients with colon lavage, gastric lavage, morphia and veratrone injections. We were then following the Rotunda line of treatment with certain alterations in the administration of sedatives. Morphia was the main sheet anchor supplemented by chloral and bromide per rectum. After the gastric lavage concentrated magnesium sulphate solution—3 ounces—was left in the stomach through the tube. This line of treatment gave us a very high mortality rate—about 30 per cent. From 1935 we gave up the stomach wash and colon lavage and stuck to the use of sedatives only—morphia injections and chloral and bromide per rectum according to a planned time schedule. We never interfered with the pregnancy in the eclamptic. Labour came on in its usual course and the maximum obstetric treatment consisted in cutting short the second stage when conditions were satisfactory for immediate delivery; i.e., when the head was on the perineum it was delivered by forceps or a breech was extracted when the os was fully dilated. No forcible delivery was ever done. From 1935–1938 we treated our eclamptics on these lines and our mortality fell to 20 per cent. In 1938 we modified our treatment by adding to the sedative line of treatment artificial rupture of membranes as Stroganoff himself had done. We started to rupture the membranes artificially

when we found that the sedatives were unable to control the convulsions. At first we did it only in those cases where the cervix was effaced and partially dilated and the presenting part engaged. But as we gained more and more experience and watched the improving results, we began to rupture the membranes artificially in all cases of eclampsia classed as severe according to the London Committee's classification, irrespective of the nature of the cervix and the station of the presenting part. In other words, we started to rupture the membranes artificially even in those primiparae with unengaged heads and a closed cervix which was not taken up except when there was cephalo-pelvic disproportion. We had no cause to regret this attitude. The results obtained were definitely more satisfactory and our observations were published in this Journal (Mudaliar, Nair and Menon, 1940). We changed from one sedative to another and to a combination of sedatives and in all cases kept to the dictum of artificial rupture of membranes in all severe eclamptics. The sedatives we used varied from morphia ¼ gr. every 4 hours, not more than 2 grains being given in 24 hours, injections of magnesium sulphate solution (15–20 per cent), 5–10 ml. every 4 hours, chloral and bromide per rectum, or paraldehyde 7–10 ml. intramuscularly repeated in smaller doses every 4 or 6 hours either alone or in combination with morphia. We tried all these sedatives except rectal bromethal. Also we started using from 1938 intravenous injections of 20–25 per cent glucose solution as a routine. Our attitude to labour continued to be conservative—namely not to interfere except to cut short the second stage. Caesarean section was forbidden except in the presence of disproportion and so we treated on these lines from 1938–1950, 1,151 cases of eclampsia. Table I below gives the maternal mortality per year. In some years with this line of treatment, we had a mortality rate of 20 per cent—in some years 8 per cent. The average for the whole series was 15·1 per cent. We realized that with this conservative line of treatment we could not cut down our mortality rate below 8 per cent. Analysis of these cases also showed that whatever sedatives we used, the recurrence of fits occurred in 47 per cent. That was the position in October, 1951.

TABLE I

Year	No. of Cases	No. of Deaths	Percentage
1938 ..	86	16	18·5
1939 ..	83	12	14·5
1940 ..	55	11	20
1941 ..	70	6	8·4
1942 ..	21	3	12·8
1943 ..	61	8	13·2
1944 ..	66	7	10·6
1945 ..	85	11	12·8
1946 ..	108	20	18·5
1947 ..	107	21	19·6
1948 ..	104	19	18·2
1949 ..	166	28	26·9
1950 ..	139	12	8·6
Total ..	1,151	174	15·1

At this stage I thought we should try out the sodium-thiopentone-dextrose therapy advocated by the late Professor O'Donel Browne of the Rotunda Hospital. He had just then published a series of 18 cases treated in 2 years with a low mortality—5·5 per cent. Seventy-five patients were treated on the lines suggested by Professor Browne. The details of the treatment and my observations were published in this Journal (Menon, 1953). From my experience with this line of treatment, I concluded that while sodium-thiopentone is perhaps the best drug in the control of convulsions in eclampsia, it did not in any way in my series of cases help to reduce the maternal mortality. There were 12 deaths in this series of 75 cases—a mortality rate of 16 per cent. And so in 1952 I gave up the sodium-thiopentone-dextrose therapy.

Now followed a period of indecision. With the failure of sodium-thiopentone-dextrose therapy I realized that our results cannot be improved further by the conservative line of treatment in whatever shape it is adopted. I again made a detailed study of the 174 maternal deaths among the 1,151 cases treated from 1938–1950. Two important facts stood out: firstly, that ante-partum eclampsia has the maximum mortality (Table II)—17 per cent as against 9 per cent for post-partum and 6 per cent for intra-partum eclampsia. Secondly, that in the severe type of eclampsia the longer the time interval between the onset of fits and

TABLE II

Type of Eclamptics	No. of Cases	No. of Deaths	Per-centage
Ante-partum ..	826	145	17·5
Intra-partum ..	61	4	6·5
Post-partum	264	25	9·3

delivery, the greater the mortality (Table III). Many writers may not agree on these points, for according to most post-partum eclampsia has the maximum mortality. My findings in a large series do not confirm these views. Forty of our ante-partum eclamptics died undelivered.

TABLE III

Time from First Convulsions to Delivery	Average Mortality Percentage
0– 2 hours	7
2– 4 hours	12·8
4– 8 hours	18·6
8–12 hours	22
12–18 hours	25
18–24 hours	32
Over 24 hours	42
Died undelivered	4·3

These facts, combined with the improvement that follows delivery in most cases of ante-partum eclampsia, which all have often noticed, made me consider the question of quick termination of pregnancy in these severe ante-partum eclamptics. All are agreed that, in the severe type of pre-eclamptic toxaemia, emptying the uterus by Caesarean section often saves the mother and baby. Could not this treatment be extended to the severest form of toxaemia, i.e., eclampsia? Caesarean section for eclampsia stood condemned from its early days because of the high maternal mortality associated with this procedure. But then those were the days when lower segment Caesarean section was in its infancy, anaesthesia was poorly developed and antibiotics unknown. Further, as the years roll by, more and more evidence is accumulating pointing to the placenta as a major aetiological factor in toxaemia. If that be so, so long as the placental circulation is alive, so long will the toxic products responsible for the toxaemia continue to enter the maternal circulation and damage the vital organs, the liver, kidneys and brain. If the patient is to survive the eclampsia, the removal of the causative factors must be effected before irreversible changes are produced in the vital organs. In other words, there would be a case for rapid emptying of the uterus in these cases—especially in the severe eclamptics. At present for such rapid emptying there is, under modern surgical conditions, no better method than a lower segment Caesarean section. Artificial rupture of membranes may be good enough to accelerate labour in those eclamptics who are already in labour but in those with unripe cervices and unengaged heads there is often a long latent period before labour sets in, which would be disadvantageous to the ultimate result. Hence I decided to try out planned Caesarean section as a method of treatment for eclampsia.

The principles of treatment were laid down as follows: all eclamptics on admission are given a sedative, ¼ gr. morphia, and a general and obstetric examination made. A vaginal examination also is done to find out whether the patient is in labour or not. All cases of severe ante-partum eclampsia—classified severe according to the London Committee's classification—in whom the cervix is uneffaced and closed and presenting part unengaged are delivered by a lower segment Caesarean section under local infiltration anaesthesia. If the vaginal examination reveals that the labour has commenced, the membranes are ruptured artificially to hasten the progress of labour. The mild eclamptics are kept under observation after a sedative (morphia). If the fits recur and the patient is not in labour, they are submitted to Caesarean section. Post-partum eclamptics are treated on the usual sedative lines. In all cases the sedatives are given as in the conservative treatment on a planned time schedule. In addition all patients are given 2 pints of 25 per cent dextrose in 24 hours and penicillin prophylactically.

On these lines I treated the next series of 105 cases. No selection of cases was made and the principles laid down were rigidly observed. The 105 cases were distributed as follows:

Post-partum	24 cases
Ante- and intra-partum ..	81 cases

I have grouped the ante- and intra-partum cases together as in many a case brought from outside with a history of fits, on admission the patients were in active labour. It is possible these fits might have started ante-partum, but by the time they were brought to the hospital, labour had started in many a case. Out of these 105 cases, I lost 6—a gross maternal mortality of 5·3 per cent. If I am permitted to exclude one patient who came in with advanced bilateral pulmonary tuberculosis and severe eclampsia who died within 6 hours of admission, I have in this series only 5 deaths out of 104 cases—a mortality rate of 4·8 per cent.

Twenty-five Caesarean sections were done in this series. I lost 1 patient—she was a severe eclamptic—with a temperature of 102·4° F and pulmonary oedema on admission. She died 18 hours after the operation.

All these were lower segment Caesarean sections under local infiltration anaesthesia. 100 mg. of Pethidine with 1/150 gr. of hyoscine hydrobromide are given intravenously as premedication half-an-hour before the operation. In 6 patients there was recurrence of fits—1 fit each in 4 patients and 3 fits each in 2 patients. They were very mild. The convalescence in all cases was surprisingly smooth and uneventful. One patient developed anuria—the blood urea going up to 248 mg. on the sixth day. She was treated according to the method of Bull. On the ninth day diuresis was established and the patient survived.

Twenty-three babies were born alive. Three babies died in the neonatal period due to prematurity. The gross foetal mortality rate was 20 per cent.

Out of 24 post-partum eclamptics, 3 died and 1 was an intra-partum eclamptic in whom artificial rupture of membranes was done. In spite of sedatives, she continued to have fits—52 in number—and died 24 hours after delivery.

According to Williams the condition in which patients would suffer the least from lack of medical attention was eclampsia. Eastman (1950) records cases of eclampsia in Chinese women who have survived after days of convulsions resulting in spontaneous labour and survival without any medical attention. All of us have seen such cases. "By writing these facts", writes Eastman, "I do not mean to advocate a policy of therapeutic nihilism in eclampsia, but wish simply to recall that this disease like many others showed a strong tendency to spontaneous abatement provided the patient is not killed by obstetric trauma or overtreatment." Quoting the figures from Johns Hopkins Hospital, Eastman concludes, "the immediate treatment of eclampsia today then is not concerned with the question of obstetric interference, but is simply a matter of determining the particular form of conservative therapy which is to be employed".

"If there is one thing that is settled in the treatment of eclampsia, it is that Caesarean section routinely preferred gives the highest maternal mortality", writes Greenhill (1947), and Dieckmann (1952) remarks "Caesarean section is performed if there is cephalopelvic disproportion or if the eclampsia is severe and the cervix is closed and uneffaced".

Morris and Dewar (1947) during their trials with rectal bromethal in eclampsia recommend Caesarean section in cases where prompt uterine response to artificial rupture of membranes was unlikely as judged by the nature of the cervix on vaginal examination.

From the limited number of Caesarean sections I have done for eclampsia, two things have struck me: (1) Caesarean section in the eclamptic under modern conditions is not so very dangerous to the mother, (2) the remarkable improvement in the patient within 24 hours of the section. If Caesarean section is to give the best result, it must be done at the optimum time and not as a last resort when conservative treatment has failed to control the convulsions. Once the irreversible changes have been produced in the vital organs by the toxaemia, nothing will save the patient and so *Caesarean section must not be withheld to the end*. The criticism of this line of treatment is obvious—namely that we might be doing unnecessary Caesarean section in patients who might have responded to persistent conservative treatment. It may be so; but eclampsia is so fickle a disease that one often finds the prognosis upset. It is so uncertain in its course and its response to treatment. And it is exactly this uncertainty of the course of the disease and the obscurity of its aetiology that

justifies in my opinion a Caesarean section even early in the disease.

I do not wish to be misunderstood. I am not advocating routine Caesarean section for eclampsia. All the conclusion that I draw from this series is that the sinister reputation of Caesarean section in eclampsia is under modern conditions unfounded and that, in the severe ante-partum eclamptic with a closed uneffaced cervix and unengaged presenting part, it might give better results if conservative treatment is supplemented by timely Caesarean section instead of withholding it. I believe that Caesarean section in such cases does not materially add to the inherent mortality in such eclamptics. On the other hand I make bold to suggest that done at the proper time Caesarean section may help in reducing the maternal mortality in these cases.

I have also to point out the mortality in eclampsia varies; every year with the same line of treatment one gets varying rates, sometimes high, sometimes low. It is possible that this series coincided with one of those natural lucky variations. Hence more cases have to be done before a final conclusion can be drawn. All the same I realize that there is a definite place for Caesarean section in eclampsia.

Summary and Conclusion

The results of conservative treatment of eclampsia in 1,151 cases are presented.

A case is made out for Caesarean section in eclampsia in combination with the sedative line of treatment.

One hundred and four cases were treated by the combined method with only 5 deaths. Out of 25 Caesarean sections done in this series only 1 was lost.

My thanks are due to Dr. R. K. K. Tampan, Director and Superintendent, Government Hospital for Women and Children, Egmore, Madras, for giving me all facilities to carry out this work.

References

Dieckmann, W. J. (1952): *Toxemias of pregnancy*. 2nd ed. Mosby, St. Louis.

Eastman, N. J. (1950): *Williams' Obstetrics*. 10th ed. Appleton Century, New York.

Greenhill, J. P. (1947): *DeLee's Principles and practice of obstetrics*. 9th ed. Saunders, Philadelphia.

Menon, M. K. K. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 710.

Morris, W. I. C., and Dewar, J. B. (1947): *J. Obstet. Gynaec. Brit. Emp.*, **54**, 417.

Mudaliar, A. L., Nair, A. S. M., and Menon, M. K. K (1940): *J. Obstet. Gynaec. Brit. Emp.*, **47**, 307.

Stroganoff, W. (1928): *Proc. R. Soc. Med.*, **21**, 1734.

BOWEN'S DISEASE OF THE VULVA

Report of 2 Cases

BY

F. HAMILTON LECKIE, *M.C., T.D.*, L.R.C.P., M.R.C.O.G.

Assistant Obstetrician

Eastern District Hospital, Glasgow

IN 1943 Knight reviewed the literature on Bowen's disease of the vulva, traced reports of 26 cases, and added 6 new ones. Huber, Gardiner and Michael (1951), differentiating between this condition and Paget's disease of the vulva, apparently found reports of 12 authentic cases of the latter, and added 3 new ones. A further case of Paget's disease of the vulva has been described by Paget and his colleagues (1954). Jeffcoate, Davie and Harrison (1944) have questioned the scientific basis of separating cases of intra-epidermal carcinoma of the vulva into Bowen's disease and Paget's disease, and describe 2 cases as the former condition. In considering malignancy of the vulva, Graves and Mezer (1942) mention the pathology in 56 of 58 cases as being epidermoid, but give no indication as to how many were intra-epidermal. Gardiner *et al.* (1953) assume that invasive carcinoma of the vulva is preceded by an intra-epithelial phase, and base their report on a study of 8 cases and a review of a total of 112 cases of carcinoma of the vulva: in this report 2 cases of intra-epithelial carcinoma persisted for 7 and 11 years before invasion occurred; in 2 cases there were large intra-epithelial lesions with early central invasion; and 4 cases were grossly characteristic of invasive carcinoma with microscopic evidence of intra-epithelial carcinoma of the periphery of the invasive neoplasm. From this report it is difficult to determine the exact number of cases which may be classed as true Bowen's disease of the vulva; it would appear that 2 only were intra-epithelial and non-invasive for a known time. If one accepts the view that intra-epidermal carcinoma of the vulva should be separated into 2 groups, it would appear that some 36 cases of Bowen's disease, and 16 cases of Paget's disease have been reported: if the view held by Jeffcoate and his co-workers is subscribed to, about 52 cases of intra-epidermal carcinoma (Bowen's disease) of the vulva have been described. In either event, it may be accepted that the condition is apparently quite rare in gynaecological practice, and the additional cases now reported may be of interest.

CASE REPORTS

Case 1

The patient, a married woman aged 42 years, was first seen at the gynaecology clinic of the Eastern District Hospital, Glasgow, on 24th February, 1954. She complained of a small sore at the "inside of the front passage"; this was rather painful, especially during menstruation, and had been present for about 2 months, she having noticed it about mid-December, 1953. On further questioning she stated that the first thing she had noticed was irritation—pruritus vulvae. She applied some cream and soon afterwards she noticed the "lump". This lump became painful and grew larger. Later there was occasional slight bleeding from the sore.

Menstruation commenced when she was aged 16 years, the loss had always been quite heavy, recurred at intervals of 28 days and lasted for 3 to 4 days. Her last menstrual period commenced on 20th March, 1954.

She had been married for 15 years and had been pregnant on 2 occasions, having normal, full-time pregnancies and spontaneous deliveries in 1939 and 1942. In 1950 she had been admitted to this hospital, when a vaginal plastic repair operation had been performed. She had not otherwise had any illnesses of note, and the remainder of her history was irrelevant. The Wassermann reaction was negative.

On examination of the vulva a flat, slightly raised, plaque-like tumour was seen about the middle of the inner aspect of the left labium majus, and extending on to the outer aspect of the left labium minor; it was roughly circular in shape and was about the size of a shilling—about ½ inch (1·25 cm.) in diameter, and was vertically creased about its middle. At one point on the upper outer quadrant there was a small area which was

FIG. 1

Case 2. Photograph of vulvar papilloma to show size, appearance and situation.

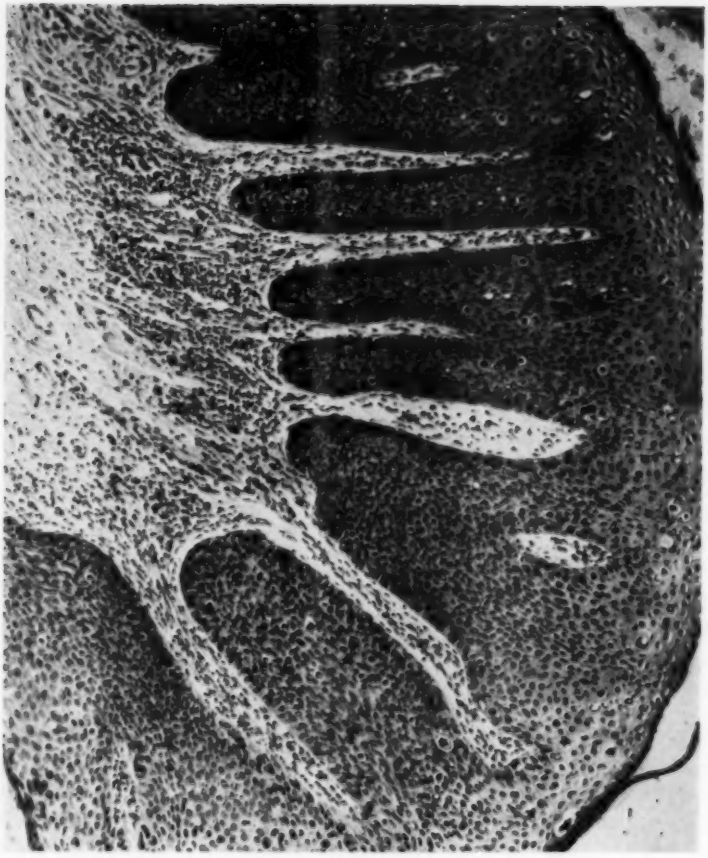


FIG. 2

Case 1. Section of vulval papilloma showing elongation of the interpapillary epithelial masses, loss of stratification, many mitotic figures, and inflammatory changes in the dermis. H. & E. ×550.

FIG. 3

Case 2. Section of vulval papilloma showing features similar to those of Case 1, but, in addition, there is hyperkeratosis and many of the cells have irregular nuclei of giant form. H. & E. ×550.

more exuberant and obviously papillomatous. Bimanual examination did not reveal the presence of any gross abnormalities apart from a cystic right ovary—during a subsequent examination this was ruptured. Glandular masses were not detected. Arrangements were made to admit the patient to hospital for operation.

After admission to Eastern District Hospital on 12th April, 1954, the history and examination findings were as before. On 13th April with the patient anaesthetized, the labial tumour was removed by wide local excision, a vertical ellipse of tissue about 3 inches (7·5 cm.) by 2 inches (5 cm.), centred on the tumour, being removed.

Pathologist's Report

No. E.1773/54. 19th April, 1954.

"Naked eye. Ragged ellipse of fissured skin bearing an oval plaque of raised pigmented papillary growth. Received fixed.

"Microscopical examination. In structure this is carcinoma which is still confined to the epidermis. It corresponds to Bowen's disease, a pre-cancerous dermatosis. The pigmentation is due to melanin which is seen in the stratum basale cells and in the superficial part of the corium."

Case 2

The patient, aged 32 years, and married for 5 years, was seen first at one of the antenatal clinics at Eastern District Hospital, Glasgow, on 31st August, 1953, when she was pregnant for the third time, cyesis being about 4½-months duration.

Her Wassermann reaction was negative, her blood group was O(4), and she was rhesus positive. At 18 years she had had her appendix removed, and about the same time there was some question of the possibility of her having pulmonary tuberculosis. Apart from this there was nothing relevant. Menstruation commenced at 14 years of age, and had always been regular, recurring every 28 days, the flow being rather heavy and lasting for 3 to 5 days. Normally she did not have any intermenstrual discharge. She had been pregnant on 2 previous occasions, in 1951 and 1953; these pregnancies had been normal and full-time.

During this latest pregnancy, on 5th October, 1953, she complained of some vaginal discharge, for which gentian violet was prescribed. From then onwards the discharge improved, and she remained otherwise well throughout pregnancy. On 24th December, 1953, she was admitted to this hospital in labour, and soon afterwards delivered herself of a live male child weighing 6¼ pounds (2·8 kg.); labour was normal, and the delivery was spontaneous. Soon after confinement she complained of pain on the right side of the vulva in the region of the labium majus. Local examination did not reveal any cause for this, and the puerperium continued without event.

On 10th February, 1954, the patient attended the postnatal clinic. Pelvic examination revealed an apparently normal vulva: bimanually, the uterus was in a normal position, but was found to be bulky; the cervix was lacerated. A degree of sub-involution was diagnosed, and for this pil. ergot, grains 3, t.i.d. for 5 days, was prescribed. On 3rd March, 1954, the patient returned to the clinic as requested. Discharge per vaginam previously present had now almost completely disappeared. She now complained again of pain on the right side of the labium at the clitoris. Inspection of the vulva revealed the presence of a flat, papillomatous tumour of about the size and shape of a shilling—about ¼ inch (1·25 cm.) in diameter—on the right side of the prepuce of the clitoris. She was admitted for operative treatment and on 23rd April a simple vulvectomy was carried out.

Because of the similarity between these two cases, sections from each were shown to Dr. A. D. Telford Govan, Director of Research, Royal Maternity and Women's Hospital, Glasgow. He stated that they were almost identical histologically, and he issued the following report to cover both: "The specimen consists of a papillomatous type of growth showing marked hyperplasia of the epithelium with downgrowth of the interpapillary processes. There is considerable keratinization of the superficial layers but this varies in degree in different parts of the tumour. Perhaps the most striking feature in this layer is the retention of nuclei by the cornified cells. The normal stratification of the epithelium has disappeared and the cells are polygonal even in the most superficial layers. Mitoses are common and are distributed throughout the thickness of the epithelium instead of being confined to the basal layers, as in normal epithelium. In general the epithelial cells are increased in size, and some are of giant variety with very large irregular nuclear masses. The underlying connective tissue is loose and vascular, and is infiltrated by large numbers of plasma cells and lymphocytes. All of these features are typical of intra-dermal carcinoma or Bowen's disease." (Figs. 2 and 3.)

DISCUSSION

There is little doubt that these cases are examples of Bowen's disease of the vulva, and they would appear to fulfil the criteria laid down by Knight (1943) for the diagnosis of the condition, namely—hyperkeratosis and parakeratosis, acanthosis with marked thickening of the rete Malpighii, loss of stratification of the individual cells with disorientation, the presence of nuclear clumping, "corps rondes", nuclear "grains" and mitotic figures, an intact basement

membrane, and marked vascularity of the subpapillary zone with round cell infiltration.

Apart from the relative rarity of the condition it seems that the interest of these cases is threefold. First, the short duration of the condition—in both cases about 2½ months. Second, from the clinical aspect it is interesting to note that the presenting symptoms were irritation or pruritus vulvae, although in Case 2 this was at first described as pain; this was then followed soon afterwards by the appearance of a "sore", and actual pain. In Case 1 the pain was aggravated by menstruation, and this suggests that hyperaemia may play as large a part as secondary infection in the production of pain in these conditions. Later, in Case 1, there was slight, occasional bleeding. This follows the sequence considered most common by Cosbie (1949) and Palmer, Saduger and Reinhard (1949). Third, from the point of view of treatment, although the condition is malignant, it is so locally. There is no infiltration, and the regional lymph channels are not involved, so that local excision alone should be adequate. In Case 2, treatment by vulvectomy seems to have been rather drastic in the light of histological examination and particularly in view of the age of the patient. It is suggested, therefore, that where a vulval papilloma is not obviously carcinomatous, treatment in the first instance should be by local excision alone, any further radical interference being determined by the microscopic appearances of the tumour.

Summary

A short résumé is given of the literature dealing with Bowen's disease of the vulva, and from this it is considered that the condition is relatively uncommon in gynaecological practice.

Two cases of Bowen's disease of the vulva are described, and points of interest are noted.

I have to thank Dr. Hugh Stirling for permission to publish, and Dr. A. D. Telford Govan for the pathology report, helpful criticism and advice.

References

Cosbie, W. G. (1949): *Canad. med. Ass. J.*, **60**, 64.

Gardiner, S. H., Stout, F. E., Arbogast, J. L., and Huber, C. P. (1953): *Amer. J. Obstet. Gynec.*, **65**, 539.

Graves, S. C., and Mezer, J. (1942): *Amer. J. Obstet. Gynec.*, **43**, 1016.

Huber, C. P., Gardiner, S. H., and Michael, A. (1951): *Amer. J. Obstet. Gynec.*, **62**, 778.

Jeffcoate, T. N. A., Davie, T. B., and Harrison, C. V. (1944): *J. Obstet. Gynaec. Brit. Emp.*, **51**, 377.

Knight. R. van D. (1943): *Amer. J. Obstet. Gynec.*, **46**, 514.

Paget, G. E., Rowley, H. A., and Woodcock, A. S. (1954): *J. Path. Bact.*, **67**, 256.

Palmer, J. P., Sadugor, M. G., and Reinhard, M. C. (1949): *Surg. Gynec. Obstet.*, **88**, 435.

ERRORS IN THE DETERMINATION OF URINARY PREGNANEDIOL

BY

M. G. COYLE, M.B.

F. L. MITCHELL, B.Sc., Ph.D.

C. S. RUSSELL, F.R.C.O.G.

AND

C. G. PAINE, M.D.

From the University Department of Obstetrics and Gynaecology and the Endocrine Unit United Sheffield Hospitals

THE estimation of pregnanediol in the urine of non-pregnant and pregnant women has been used for some time past in the diagnosis of anovulatory cycles, the early diagnosis of pregnancy and as a guide in the treatment of habitual and threatened abortion and pregnancy toxaemia (Guterman, 1944, 1945; de Watteville, 1951). Davis and Fugo (1947) and Michie (1953) have shown that there is a wide variation in the average daily output of pregnanediol in normal pregnancy in different women, while Bradshaw and Jessop (1953) demonstrated a daily variation in the same individual. This was more marked in the later weeks of pregnancy. Both Marrian (1949) and Swyer (1949), however, have stressed that because of the inaccuracy of the methods of assay so far available and the incomplete excretion of progesterone as pregnanediol, a most cautious and critical attitude must be taken in the interpretation of these assays.

This paper presents the results of a study of the variations in the excretion of pregnanediol in late pregnancy and a detailed examination of the accuracy of the two methods of assay used, together with a brief review of previous experiences with these methods in the light of the results obtained.

METHODS FOR THE DETERMINATION OF URINARY PREGNANEDIOL

All the available methods for the estimation of urinary pregnanediol were investigated. As the final measurement depends on either a non-specific colour reaction obtained by adding concentrated sulphuric acid to a dried residue, or weighing the residue, the purity of this residue determines the specificity of the assay. De Watteville (1951) washed the residue with cold ether to remove the greater part of the pigment. The impurities, however, are invariably oily in nature and the pregnanediol often dissolves wholly or partly in this oil; in our experience the washings with cold ether to remove the oil contained 20–30 per cent of the amount of the pregnanediol finally estimated, when tested by the method of Hodgins (1953). These findings are similar to those of Bradshaw and Jessop (1953) who investigated the washing of extracts with light petroleum.

All methods except that of Sommerville, Gough and Marrian (1948) were discarded because of their failure to give a white crystalline end product. The methods finally chosen were as follows:

Method 1

The method of Sommerville, Gough and Marrian (1948) was used without major modification. The urine (500 ml.) after acid hydrolysis was extracted with toluene, and any emulsion obtained was broken by the addition of a few drops of Teepol (Shell Chemicals, Ltd., London) instead of the tedious filtration procedure used by Sommerville and his colleagues; this modification was shown not to interfere with the extraction. The toluene extract was washed with *N*-NaOH and water, and evaporated to dryness; the residue was then dissolved in

ethanol and precipitated under carefully controlled conditions of time and temperature, once with 0·1 *N*-NaOH and twice with water, the precipitate in each case being collected by centrifugation with the aid of Hyflo Super-Cel (Johns Manville Co., Ltd., London). After a final decolorization with charcoal in ethanol, concentrated sulphuric acid was added to a portion of the dried extract and placed for 24 minutes in a water bath at 25°; the absorption of the solution was then measured in the Spekker Photoelectric Absorptiometer using an Ilford Spectrum Violet 601 filter (transmission max. 430 mμ). In addition to this colorimetric assay the remainder of the dried extract was weighed to give an alternative method of estimation.

As the controlled precipitation technique in Method 1 was very laborious and time-consuming for a routine method, the possibility of dispensing with this procedure was investigated. The shortened technique of Sommerville, Marrian and Kellar (1948) was not chosen because, in agreement with Smith (1950), it was found that this method did not always give a white crystalline final product.

Henderson, Maclagan, Wheatley and Wilkinson (1949) used a precipitation from acetone, because this solvent appeared from preliminary work to give the best results. They showed that the time and temperature of precipitation were not determining factors in the recovery of added pregnanediol, and, as pregnanediol is less soluble in acetone than in ethanol, recovery from acetone should compare favourably with that obtained by the method of Sommerville, Gough and Marrian (1948).

In the original method used by Henderson *et al.* (1949) only one precipitation was carried out; for Method 2, the two techniques have been combined, in that three precipitations from acetone instead of ethanol were used.

Method 2

The dried toluene residue obtained as for Method 1 was taken up in 2·5 ml. acetone in a 50 ml. centrifuge tube and 50 ml. 0·1 *N*-NaOH was added. The mixture was stirred and placed in a boiling water bath for 10 minutes and subsequently transferred to a refrigerator at 4° for 2 hours. Hyflo Super-Cel (10 mg.) was then added with stirring and the tube was centrifuged at 2,500 r.p.m. for 20 minutes. The supernatant liquid was decanted and the precipitation twice repeated on the residue using distilled water instead of 0·1 *N*-NaOH. The remainder of the procedure was as for Method 1.

Recovery experiments were carried out for comparison with Method 1. One precipitation, using pure pregnanediol, pure solvents and 0·1 *N*-NaOH or distilled water, gave similar results for both methods: but when pure pregnanediol was added to male urine (0·5–2·0 mg. added to 500 ml. of urine) the recoveries using each technique in full were approximately 10 per cent less for Method 2 than for Method 1; this discrepancy was greater when pregnancy urine was examined. As it has now been shown (see later) that the final product from pregnancy urine using either method was not pure pregnanediol, this discrepancy could be due to a difference in the amount of impurity present.

Design of Experiment

Three consecutive 24-hour specimens of urine were collected from each of 10 normal primigravid patients in the 34th–35th week of pregnancy. Every care was taken to ensure a complete 24-hour specimen in each case; also the volume and creatinine content of each specimen of urine were noted and where these showed a marked daily variation the specimens were discarded and others obtained; this was only necessary on 2 occasions. Purified extracts were prepared in duplicate by separate workers, each using one of the methods already described. The pregnanediol content in each case was estimated gravimetrically, and colorimetrically after the addition of concentrated sulphuric acid. The extracts were also examined for purity by measuring their melting points and absorption of ultraviolet light. Each patient was kept under observation until delivery when the weight of the baby, and the weight, macroscopic appearance and histology of the placenta were noted.

Results

The duplicate readings were first examined and the differences between pairs of readings

analyzed. The mean difference of duplicate readings in Methods 1 and 2 was $3{\cdot}9 \pm 0{\cdot}57$ (standard error of mean of 30 observations) and $2{\cdot}5 \pm 0{\cdot}38$ (30) showing that the technical accuracy of the two methods was similar. The duplicate readings were therefore averaged, leaving 4 estimations of "pregnanediol" for each of the 10 patients on each of 3 days, making 120 estimations in all (Table I).

The marginal totals shown in Table I indicate

TABLE I

Excretion Levels of Pregnanediol in mg./24 Hours

Patients		Day 1 By Colour	Day 1 By Weight	Day 2 By Colour	Day 2 By Weight	Day 3 By Colour	Day 3 By Weight	Totals	
1	Method 1	45	93	27	65	31	56	542	
	Method 2	36	56	29	44	25	35		
2	Method 1	35	58	39	54	41	60	445	
	Method 2	17	33	23	37	21	27		
3	Method 1	37	64	50	79	56	89	512	
	Method 2	20	20	13	18	32	34		
									Method 1, 3,641
4	Method 1	55	100	61	115	53	81	671	
	Method 2	34	43	32	42	25	30		
									Method 2, 1,996
5	Method 1	53	59	54	63	52	61	503	
	Method 2	29	48	21	24	17	22		
6	Method 1	80	82	72	67	70	83	707	
	Method 2	34	70	10	57	12	70		
7	Method 1	48	64	42	53	44	57	451	
	Method 2	31	36	21	20	10	25		
									Colorimetric 2,374
8	Method 1	80	76	69	48	68	72	741	
	Method 2	48	66	47	64	35	68		
									Gravimetric 3,263
9	Method 1	48	49	64	48	52	46	449	
	Method 2	25	25	22	26	21	23		
10	Method 1	61	71	47	55	64	75	616	
	Method 2	33	55	22	54	31	48		
	Totals	2,017		1,798		1,822		5,637	

Analysis of Variance

	Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Probability
Between Days	721	2	360	2·7	0·1
Between Patients	9,416	9	1,046	7·8	Very small
Between Methods	22,550	1	22,550	170	Very small
Between Colorimetric and Gravimetric Assay	6,586	1	6,586	50	Very small
Error	14,076	106	133		
Total	53,349	119			

the main results of the experiment. There is a large difference between individual patients and a small difference (not significant) between the days, which may be ignored in view of the other and more important findings. There are marked differences between the results for Method 1 and for Method 2 and between gravimetric and colorimetric estimations, differences which are far greater than could possibly be the result of chance variation. These observations, together with the high mean square for error, suggested that all four estimates were at fault, and this was shown to be the case when the final products were tested for purity by measuring their melting point and ultraviolet absorption spectra (Table II).

The average melting point for the product of Method 1 was 207°±1·8° (standard error of mean of 32 observations), and for Method 2 219°±2·2° (41), levels which were clearly different from those of pure pregnanediol (243°), all melting points being measured on a Gallenkamp (London) stage. Though Method 1 gave estimations for pregnanediol nearly twice those for Method 2 (see totals—Table I), the higher melting point of the final extract of Method 2 indicated that this method gave the purer product.

The ultraviolet absorption spectra were measured in ethanolic solution and peaks or inflections were obtained in all cases at approximately 204 mμ and 230 mμ. The average values for $E\,\frac{1\text{ per cent}}{1\text{ cm.}}$ for Methods 1 and 2 at 204 mμ were 41±2·7 (30) and 57±5·9 (30) and at 230 mμ the corresponding values were 28±2·2 (30) and 32±3·9 (30). As pregnanediol at the concentration and within the range investigated has a negligible absorption, these peaks must have been due to impurities; the absorption measured at these wavelengths is an indication of some of the impurity present.

The large difference between colorimetric and gravimetric estimation (see totals Table I) stresses the impurity of the product and the non-specificity of the method of assay.

Study of Placentae

The relationship between the duration of pregnancy, baby's weights and placental weights are shown in Table III. Sections from representative areas were examined microscopically. The histological findings indicated that in Cases 1, 3, 4, 5, 6, 8, 9 and 10, there was no placental insufficiency, although in Cases 6 and 9 the placentae were "ageing" rapidly. In Case 8 the structural detail was so well preserved that, without reference to the clinical data available, a measure of prematurity was indicated. The histological reports on the other two cases were:

Case 2. (Foetal distress)

The trophoblast shows unusual proliferation for a full-time placenta. The proliferation is quite orderly in character. The villi generally are very small and tend to be rather cellular with a considerable amount of collagen formation. The contained blood vessels are small and frequently not opposed to the trophoblast. A few of the arterioles of the villous stalks show a proliferative endarteriolitis, but this is not a marked feature. Intravillous fibrinoid deposition is slight. In general it would be expected that this placenta would have shown considerable insufficiency.

TABLE II

Melting Points and Ultraviolet Light Absorption of Purified Extracts

	End Product Method 1			End Product Method 2			Pure Pregnanediol
	Mean	Standard Error	No. of Estimations	Mean	Standard Error	No. of Estimations	
Melting points* ..	207°	± 1·8°	32	219°	± 2·2°	41	243°
$E\,\frac{1\text{ per cent}}{1\text{ cm.}}$ at 204 mμ	41·2	± 2·7	30	56·6	± 5·9	30	0·15
$E\,\frac{1\text{ per cent}}{1\text{ cm.}}$ at 230 mμ	27·9	± 2·2	30	32·0	± 3·9	30	0·30

* Melting Points Measured on Gallenkamp (London) Stage.

TABLE III

Obstetrical Details of Cases Studied

Case No.	Duration of Pregnancy at Delivery (weeks)	Baby's Weight Pounds	Baby's Weight ounces	Placental Weight Pounds	Placental Weight ounces	Macroscopic Appearance of Placenta
1	41	8	15	1	14	Few small infarcts present.
2*	39½	6	5	1	3	Unhealthy "gritty" appearance. Long cord. No infarcts.
3	41	8	1	1	5	Few small infarcts present.
4	43	8	1	1	8	"Gritty" appearance. Few small infarcts.
5	40	4	9	1	2	Small, but healthy.
6	40	8	6	1	8	Healthy.
7†	44	9	7	1	12	Unhealthy "gritty" appearance. No infarcts.
8	38½	6	13	1	11	Healthy. Few small infarcts.
9	41	6	12	1	3	Healthy.
10	40	7	5	1	5	Healthy with few small infarcts.

* In Case 2 there was marked foetal distress, but a living child was obtained.
† In Case 7 the infant was stillborn.

Case 7. (*Stillbirth*)

The trophoblast is generally rather atrophic. The villi are normal in size and the contained blood vessels well opposed to the trophoblast. There is a considerable amount of fibrinoid deposition within the villi throughout, and this, in places, has resulted in small infarct formation. Many of the arterioles of the villous stalks show obliterative changes and there is considerable calcium deposition. In general this placenta is regarded as showing insufficiency.

The histological examination of the placentae shows a reasonable degree of conformity with the clinical pictures of the cases recorded. A comparison between these results and those of "pregnanediol" assay do not appear to show any measure of correlation.

Before concluding that the two methods of measuring pregnanediol described should be discarded for routine use, a careful review was made of previous experience with these assays over several years.

Review of Previous Experiences

The records of 24 gynaecological cases were available for study; infrequent or irregular menstruation or infertility were the main complaints. In all cases "pregnanediol" was estimated by Method 2. Nine of these patients had levels ranging from 0·7–4·5 mg./24 hours from the 14th–28th day of the menstrual cycle, and in all cases the endometrium showed histological evidence of progesterone activity. In 2 other cases, although "pregnanediol" was detected in the urine, the endometrium was of the hypoplastic non-secretory type. In the remaining patients, evidence of ovarian or pituitary dysfunction was detected by other endocrine assays, and no "pregnanediol" was present in the urine.

Only 2 abnormally high levels of "pregnanediol" excretion were found among 700 patients investigated, both occurring in hermaphrodite children aged 4 years. The final "pregnanediol" fraction consisted in each case of a brown oily substance instead of a white crystalline solid. The results are shown in Table IV. The ultraviolet absorption spectra showed a marked peak with a very high extinc-

TABLE IV

The Results of the Endocrine Investigation of Two Hermaphrodite Children

		Case 1	Case 2
Colorimetric Estimation of Pregnanediol mg./day	Method 1	79	24
	Method 2	51	6·4
Gravimetric Estimation of Pregnanediol mg./day	Method 1	130	—*
	Method 2	—*	29
E 1 per cent 1 cm. at 235 mμ	Method 1	80·7	—*
	Method 2	—*	71·5
17-Ketosteroid Excretion mg./day		45	11

—* = not done.

tion value in both cases at 236 mμ, thus indicating the possible presence of a large quantity of $\alpha\beta$ unsaturated ketone. Cortisone therapy (50 mg./day intramuscularly) reduced the level of excretion of this material to zero within 4 days, indicating that the substance was probably of adrenal origin. Thus false positive pregnanediol excretions were found in these cases.

The individual records of 20 cases of habitual or threatened abortion were also available for close study. Not all cases with low levels of "pregnanediol" miscarried, and in some cases with normal levels the outcome of the pregnancy was unsatisfactory. Weekly determinations were carried out on 1 patient with a history of 2 previous miscarriages. She had stilboestrol and progesterone therapy during the investigation and delivered a living child at term; the "pregnanediol" excretion in this case varied markedly from week to week.

In a few cases of pre-eclamptic toxaemia where an attempt had been made to use the estimation as a measure of placental function, marked variation in the results obtained rendered this impossible. Thus in 2 cases where the patients delivered living premature babies at 34/35 weeks the urinary "pregnanediol" excretion levels were 5·6 and 6·5 mg./24 hours respectively.

Discussion

The work reported here shows clearly that the estimation of urinary pregnanediol by the above techniques, which were chosen as being the most satisfactory available, must be of very doubtful clinical value. Considerable variation has been shown in the level of excretion of "pregnanediol" in normal pregnancy between individuals and possibly a small variation from day to day in the same individuals. A marked variation was apparent when comparisons were made between the two methods of obtaining the purified extract and between the two methods of estimating the pregnanediol content. There was also a high error variation. The melting points and absorption spectra of the end products together with the difference in values obtained by colorimetric and gravimetric estimation indicate that much of this variation is due to the presence of impurity. This has been proved in the past to give fictitiously high results for most of the shorter methods for estimating pregnanediol based on the procedures of Astwood and Jones (1941) and Talbot, Berman, MacLachlan and Wolfe (1941).

In the light of these errors a careful reassessment of previous experience with these methods of assay was undertaken lest any useful clinical correlation be overlooked. None was found. The variation in the results in cases of habitual and threatened abortion and pre-eclamptic toxaemia made it impossible for the test to be used as a diagnostic or prognostic aid in the cases cited.

In gynaecology false positive results for pregnanediol were obtained in 2 cases in which the endometrium was of the hypoplastic non-secretory type and in 2 cases of hermaphroditism in children. These observations are in line with that of Swyer (1949) who stated "The total excretion of pregnanediol in the luteal phase of the menstrual cycle was so variable that one cannot hope to give indisputable evidence of corpus luteal activity".

Proof has been obtained to show that much of the unreliability of the assay of urinary pregnanediol is due to the non-specificity of the techniques employed. It remains to be shown whether a more specific technique will give a reliable indication of body progesterone level. If such a technique be found then much may be gained. A reliable measure of placental function in early and late pregnancy would be invaluable in clinical practice.

Summary and Conclusions

The levels of urinary pregnanediol excretion in late pregnancy have been studied by the methods of assay at present available.

In a planned study of the variations in these levels, estimations were made on the 24-hour urine specimen of each of 10 normal 34–36 week primigravid women on each of three consecutive days. Purified extracts from each urine sample were prepared by 2 selected methods and the "pregnanediol" content estimated both gravimetrically and colorimetrically.

The 4 methods of assay gave widely different results which have been analyzed by the analysis of variance.

The difference between results obtained by the

two methods and by gravimetric and colorimetric assay were highly significant.

The melting points and ultraviolet light absorption of the purified extracts were also investigated and were found not to be those of pure pregnanediol.

It is concluded that the impurities present in the purified extracts account for much of the variation in the results obtained and for the high level of uncontrollable error.

A review to determine any clinical value of these assays—whatever they measure—carried out over several years, did not reveal any clear evidence of usefulness which might be set against the errors above described.

In our opinion, therefore, the above methods should be discarded for routine assays of pregnanediol.

New methods of measuring pregnanediol require to be sought and carefully studied.

Acknowledgments

We wish to thank Mr. L. B. Patrick for his interest and encouragement in this work, and the medical staff of the Jessop Hospital for Women, Sheffield, for their cooperation in the selection of the patients. We are also grateful to Mr. T. E. Durrant, Mr. R. Hall, and Mr. R. G. Hodgins for much expert technical assistance. A grant from the Board of Governors of the United Sheffield Hospitals, which we gratefully acknowledge, made this work possible.

References

Astwood, E. B., and Jones, G. E. S. (1941): *J. biol. Chem.*, **137**, 397.

Bradshaw, T. E. T., and Jessop, W. J. E. (1953): *J. Endocrinol.*, **9**, 427.

Davis, M. E., and Fugo, N. W. (1947): *Proc. Soc. exp. Biol., N.Y.*, **66**, 39.

Guterman, H. S. (1944): *J. clin. Endocrinol.*, **4**, 262.

Guterman, H. S. (1945): *J. clin. Endocrinol.*, **5**, 407.

Henderson, J., Maclagan, N. F., Wheatley, V. R., and Wilkinson, J. H. (1949): *J. Endocrinol.*, **6**, 41.

Hodgins, R. G. (1953): Private communication.

Marrian, G. F. (1949): *Trans. 12th Brit. Congr. Obstet. Gynaec.*, p. 110.

Michie, E. A. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 561.

Smith, O. W. (1950): *J. clin. Endocrinol.*, **10**, 496.

Sommerville, I. F., Gough, N., and Marrian, G. F. (1948): *J. Endocrinol.*, **5**, 247.

Sommerville, I. F., Marrian, G. F., and Kellar, R. J. (1948): *Lancet*, **2**, 89.

Swyer, G. I. M. (1949): *Trans. 12th Brit. Congr. Obstet. Gynaec.*, p. 114.

Talbot, N. B., Berman, R. A., MacLachlan, E. A., and Wolfe, J. K. (1941): *J. clin. Endocrinol.*, **1**, 668.

de Watteville, H. (1951): *J. clin. Endocrinol.*, **11**, 251.

PALMAR SWEATING IN PREGNANCY

BY

P. C. B. MACKINNON, M.B., Ch.B.

Department of Anatomy, Middlesex Hospital Medical School

AND

I. L. MACKINNON, M.B., Ch.B.

Department of Anatomy, King's College, University of London

DURING the luteal phase of the menstrual cycle palmar sweating is "significantly" suppressed (P. C. B. MacKinnon, 1954a), presumably as a preliminary to pregnancy. The present investigation was made to find if a further alteration occurs in palmar sweating when pregnancy is realized.

METHODS

Records of palmar digital sweat glands in the pad of the right middle finger were obtained by means of plastic prints (Sutarman and Thompson, 1952) from 75 healthy primiparous women, 25 in each trimester of pregnancy. The women were unselected except for age which was restricted to 19–25 years in order to minimize gerontological effects (P. C. B. MacKinnon, 1954b) and to permit comparison with observations previously made during the luteal phase of the menstrual cycle (P. C. B. MacKinnon, 1954a). The prints were made after half an hour's rest, between 9.30 a.m. and 11.30 a.m. during the months of January, February and March in a room whose air temperature was 65–73° F. The number of active sweat glands in 4 sq. mm. immediately distal to the central whorl was counted in each print under a magnification of 10 and recorded in Table I, along with the average count for each trimester.

Statistical comparison was made between the average number of active sweat glands obtained during pregnancy and the average number previously obtained during the luteal phase of the menstrual cycle (P. C. B. MacKinnon, 1954a). The statistical relationship between the average number of active sweat glands in each trimester of pregnancy was also investigated.

TABLE I

The Number of Active Sweat Glands in 4 sq. mm. of Skin Immediately Distal to the Central Whorl of the Right Middle Finger of 75 Pregnant Women

	1st Trimester		2nd Trimester		3rd Trimester	
	64	70	75	83	83	81
	64	40	64	82	99	72
	87	65	21	90	101	118
	70	74	83	72	59	43
	92	63	9	118	48	68
	37	84	81	105	107	63
	70	101	69	93	50	23
	48	76	85	100	70	57
	57	53	89	109	38	58
	50	58	89	55	58	82
	124	49	100	65	33	59
	98	56	61	65	88	87
	46		36		70	
Average per Trimester	68		77		65	

RESULTS

Table I shows that the number of active sweat glands in 4 sq. mm. of the skin immediately distal to the central whorl of the right middle finger varied during pregnancy from a minimum of 9 to a maximum of 124. The average was calculated to be 70. During the luteal phase of the menstrual cycle the average number was 85 (P. C. B. MacKinnon, 1954a). The difference of 15 is "significant" because it is more than twice the standard error which was calculated to be 3·6 (Hill, 1950).

Therefore the number of sweat glands in the chosen area of skin was "significantly" smaller during pregnancy than during the luteal phase of the menstrual cycle.

Table I also shows that the average number of active sweat glands was smaller during the 1st and 3rd trimesters than during the 2nd trimester. The actual difference between the counts of the 1st and 2nd trimesters is 9 with a standard error of 5·9, and the actual difference between the counts of the 2nd and 3rd trimesters is 12 with a standard error of 7·7. In neither case does the actual difference exceed twice the standard error and the observation that sweating is suppressed more during the 1st and 3rd trimesters than during the 2nd trimester of pregnancy is therefore not "significant".

Discussion

P. C. B. MacKinnon (1954a) suggested that the suppression of sweating which characterizes the luteal phase of the menstrual cycle is a reflection of increased suprarenal cortical activity, and the question now arises as to whether or not the further suppression during pregnancy is a reflection of a further increase in suprarenal activity. Evidence of increased suprarenal cortical activity during the luteal phase of the menstrual cycle is indirect (Geiringer, 1951; I. L. MacKinnon, 1953; I. L. MacKinnon, 1954), but during pregnancy Venning (1946) has shown that urinary corticoids are increased and Hewitt and Van Liere (1941) have demonstrated that the ratio of adrenal weight to body weight is increased.

The greater ease with which the activity of the suprarenal cortex can be detected in pregnancy suggests that it is more active in pregnancy than in the luteal phase. It is therefore postulated that increased suprarenal cortical activity is responsible for the greater suppression of palmar digital sweating in pregnancy than in the luteal phase of the menstrual cycle.

The observation, though not "significant", that the active sweat gland counts in the 1st and 3rd trimesters were lower than in the 2nd trimester of pregnancy is of interest because it suggests that the suprarenal cortex is especially active in the early and late stages of pregnancy, that is, at the times when toxaemias occur.

Summary

(1) Counts of the active sweat glands in 4 sq. mm. of skin immediately distal to the central whorl of the right middle fingers of 75 primiparous women, aged 19–25 years, 25 in each trimester of pregnancy, were made under resting conditions.

(2) The counts were "significantly" lower than in a comparable sample of women in the luteal phase of the menstrual cycle.

(3) It was postulated that increased suprarenal cortical activity was responsible for the greater suppression of palmar digital sweating in pregnancy than in the luteal phase of the menstrual cycle.

References

Geiringer, E. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 1010.

Hewitt, W. F., and Van Liere, E. J. (1941): *Endocrinology*, **28**, 62.

Hill, A. B. (1950): *Principles of Medical Statistics*. 5th ed. *Lancet*, London. p. 244.

MacKinnon, I. L. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 878.

MacKinnon, I. L. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 109.

MacKinnon, P. C. B. (1954a): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 390.

MacKinnon, P. C. B. (1954b): *J. Neurol. Neurosurg. Psychiat.*, **17**, 124.

Sutarman, —., and Thomson, M. L. (1952): *J. Physiol.*, **117**, 51 P.

Venning, E. H. (1946): *Endocrinology*, **39**, 203.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of Council was held in the College House on Saturday, 26th March, 1955, with the President, Sir Arthur Gemmell, in the Chair.

His Excellency the Rt. Hon. Vincent Massey, Governor-General of Canada, and Dr. George W. Corner of Baltimore, have accepted the Honorary Fellowship of the College and will attend for formal admission on Friday, 22nd July, 1955.

Professor B. P. Watson of Columbia University, New York, has accepted the invitation of the Council to deliver the William Meredith Fletcher Shaw Memorial Lecture for 1955, on Friday, 23rd September, 1955.

TUMOUR REGISTRY

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

58 QUEEN ANNE STREET, LONDON, W.1

THE registry set up by the College is now in full working order and is ready to receive further additions.

THE AIM of the registry is to collect from as wide an area (geographical) as possible complete clinical and pathological data on small groups and single cases which when taken *en masse* would provide a valuable source of information.

In this way it is hoped by collecting, grouping and follow-up over the years, to obtain a better understanding of the natural history of the rare case.

Cases suitable for registration will include:

All tumours of the VULVA.

All tumours of the VAGINA.

All tumours of the FALLOPIAN TUBES.

Tumours of the UTERUS (except fibroids, adenomyomata and carcinomata).

Tumours of the OVARY (except cystadenomata and carcinomata).

CHORION CARCINOMA (epithelioma), genital or extragenital.

NOTIFICATION should be made on a special form to be obtained from the College Secretary. A copy of this form is enclosed with this issue.

HISTOLOGICAL SLIDES (in duplicate) or paraffin blocks should be sent with the form.

The pathological SPECIMEN is not required, but the surgeon in the case might be willing to offer suitable specimens to the College Museum in which it is intended to build up a collection of first-class macroscopic specimens, second to none in the world.

ARTHUR GEMMELL,
President

REPORTS OF SOCIETIES

NEWCASTLE-UPON-TYNE OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1954

A Meeting of the Newcastle-upon-Tyne Obstetrical and Gynaecological Society was held on Thursday, 7th October, 1954, in the Royal Victoria Infirmary, Newcastle-upon-Tyne. The President, Dr. William Hunter, was in the Chair.

Professor Morris gave an address on

Shoulder Dystocia

Professor Morris said it is a commonplace of the teaching schools that the aspirant to graduation in medicine must be thoroughly instructed in obstetrical emergencies. It is rightly emphasized that these emergencies are likely to be met with in general practice in circumstances where immediate action may be called for, no time being available for deep thought and discrimination. In the conduct of the final examinations in different schools, he had always found that the inquisitors attach much importance to the answers of the candidates to simple questions related to such emergencies but while many questions are asked on the haemorrhages, the toxaemias, malpresentations, contracted pelvis and so on, it is a comparative rarity to hear a question about impaction of the shoulder girdle occurring in the course of a vertex delivery.

Yet this complication is far from uncommon, and more often than not it is an unforeseen event. It is commoner in parous than in primigravid patients, and, perhaps because of this, is a particular urgency of domiciliary practice. Many of the babies die. Others are born alive with Erb Duchenne birth palsies from which recovery is not always complete. The mothers may suffer severe soft tissue damage, and, though danger to life itself is slight, it is by no means absent.

Professor Morris had given thought to the complication and hoped that the Society would be interested to have his reflections on the subject.

Normal mechanism of shoulder delivery

First he reminded the Society of the classical description of the mechanism of shoulder delivery. The generally accepted textbook teaching declares that at the beginning of normal labour the wide diameter of the shoulders, i.e., the bisacromial diameter, lies parallel to but of course much higher than the widest side to side diameter of the foetal head, i.e., the biparietal diameter. As labour progresses, the head descends, and, under the subtle influence of the rifling of the barrel of the birth canal, it rotates to bring the occiput directly to the front, so that the sagittal suture lies in the antero-posterior diameter of the pelvis, and the biparietal diameter is placed transversely. It is suggested in the classical teaching that the trunk of the child does not conform to this movement of internal rotation. The shoulders remain in an oblique diameter of the pelvis, and the neck of the baby has a very slight twist. As soon as the baby's head is born, this twist corrects itself by the sudden flick-like movement known as *restitution*, which sets the head square in relation to the shoulders and carries the occiput once more towards the side of the maternal body to which it was originally deviated.

Thereafter the trunk descends, and in the process the shoulders rotate to bring the bisacromial diameter into the antero-posterior diameter of the pelvis. The head corresponds in the movement of external rotation which carries the occiput even more towards the side it originally occupied.

Then the anterior shoulder appears at the apex of the pubic arch. It becomes fixed there, like a pivot, and the posterior shoulder is swept over the perineum by a mechanism of lateral flexion. The remainder of the trunk follows.

Professor Morris challenged this generally accepted teaching and recollected that the mechanism of delivery in the first confinement he had ever attended had differed from the teaching. Firstly, the movement of restitution simply did not occur. Secondly, when external rotation took place, it carried the occiput towards the left, although the position had been a right occipito-anterior. Subsequent experience had confirmed that his early scepticism was justified. While the classical mechanism does occur from time to time, or maybe even frequently, it is far from being the common one.

He now adhered firmly to the belief that in normal labour the movement of internal rotation of the head is more properly described as internal rotation of the child. Whatever be the original position of the occiput, once the sagittal suture reaches the antero-posterior diameter of the pelvis, the neck is seldom twisted to any extent and the bisacromial diameter is ready to enter the pelvis more or less in the transverse diameter. As the trunk descends, the shoulders rotate once more, but it is a matter of chance which shoulder rotates to the front.

Unfortunately he could offer no incontrovertible proof that the theory is correct but radiological cinematography will be available soon as a research technique, and he hoped to know one day whether he was right or wrong.

The mechanism of impaction of the shoulders

Some cases give a little difficulty when the shoulders have entered the pelvic cavity, usually because the child is large and the powers of labour fail. Very often the shoulders are found bunched up in the transverse diameter of the pelvis. Serious difficulty worthy of the name of impaction is restricted to cases in which the bisacromial diameter attempts to enter the pelvis in the

antero-posterior diameter of the brim. An antero-posterior bisacromial engagement is unfavourable, and when the shoulders are wide or the brim small, the conditions for the most serious form of impaction are present.

In such circumstances it is the entry into the pelvis of the anterior shoulder which constitutes the major difficulty. The posterior shoulder can and does slip quite easily past the sacral promontory, but the anterior one "hitches" on the upper margin of the pubes and an impasse results until it can somehow be persuaded to enter the pelvic cavity.

Professor Morris liked to think of this situation as a "posterior acromial presentation", and to compare it with the other situations in which the anterior portion of the presenting part is prevented from entering the pelvis:

(*a*) Posterior parietal presentation, the unfavourable form of asynclitism referred to as Litzmann's obliquity.
(*b*) The impacted shoulder girdle in breech presentation with extended arms, as epitomized in Faraboeuf's well-known illustration.
(*c*) The possible situation when the posterior leg is brought down in dealing with an impacted breech presentation or a transverse lie.

Aetiology of antero-posterior engagement of bisacromial diameter

The discussion of this subject must rest upon a consideration of the probabilities rather than on sound objective evidence. It may be suggested, however, that it is more likely to occur when labour starts with the child's back directed towards the mother's flank than when it is directed either towards the front of the abdomen or to its posterior wall. If it be accepted that the common engagement of the head is occipito-lateral or transverse, the back is more likely than otherwise to occupy such a location. That antero-posterior engagement of the shoulders is seen so seldom is an indication that the mechanism by which internal rotation of the foetus takes place is a peculiarly effective one.

Indeed, he suggested that persistent antero-posterior location of the shoulders at the pelvic brim is usually attributable to factors which interfere with the easy rotation of the trunk at the time when occipito-lateral or occipito-posterior positions undergo their relatively long rotations.

Discussion of the causes of failure of trunk rotation must be largely speculative. A dry-drained amnion may be important and a taut uterus clasping the child in an over-affectionate embrace may contribute. Friction between the genital passages and the foetal skin may be increased when an obese or oedematous child bulges into every crevice and cranny of its walls. The plentiful vernix of the child which has reached or may even have passed term may occasionally have a rather similar effect.

But perhaps the most obvious though not the most frequent explanation is applicable in deep transverse arrest or impacted occipito-posterior position. Manual rotations of these positions may succeed in rotating the head without rotating the trunk. In such circumstances the malposition of the head is particularly prone to recur as soon as the hand is withdrawn. But if in accordance with a practice at one time recommended the return to the original malposition is prevented by the subterfuge of rather slick application of a single blade of the forceps, the conditions for antero-posterior shoulders are ideal.

Disproportion between the shoulders and the pelvis

Disproportion between the bisacromial diameter and the conjugate is usually due to excessive development of the child. The factors associated with such over-development are subtle, but include rarities like diabetes or the pre-diabetic state and the comparatively common condition of increasing parity. Naturally, contraction of the pelvic brim may contribute to this form of disproportion; but, if such contraction is present, the case is unlikely to present an unexpected emergency, since a baby with shoulders big enough to cause trouble almost certainly has a head which will cause significant difficulty in negotiating the narrow brim, such accidents as anencephaly being excepted.

Natural mechanisms of overcoming brim impaction of the shoulders

That there is some mechanism by which the natural forces may eventually overcome the impasse is certain, though it is rare for any mother to be left to complete delivery by such a mechanism. So far as Professor Morris was aware there is no such mechanism described in the literature, but it must be related to a spontaneous rotation of the foetus which will carry the bisacromial diameter away from the conjugate into an oblique or transverse diameter. It is interesting to consider this possible mechanism alongside that which certainly does occur in breech presentation or transverse lie when the posterior leg is brought down. He did not think this ever gave rise to a genuine obstruction, for the cases which he had seen had very rapidly corrected themselves by a rotation of the foetal pelvis through 180 degrees, as a result of which the leg originally posterior came to lie anteriorly and the opposite buttock slid off the anterior portion of the pelvic brim to enter the pelvic cavity posteriorly.

The possibility of some mechanism for "compaction" or reduction in size of the shoulder girdle, which might be nicknamed "shoulder moulding" must not be discounted. Gliding movements of the scapula on the chest wall may facilitate this by allowing the shoulder to become still more rounded than is normally the case. This process would be easier if the child's arms became displaced from their supposedly customary attitude of submissive folding across the thorax. That this attitude is often undone in late labour is certain, and Zweifel's frozen section of a mother dying after delivery of the head rather suggests that "shoulder-moulding" does occur and that extension of the elbow joint may favour it.

It is not without profit to examine these possibilities, since they may shed light on possible principles of

management in a professionally conducted confinement. The attempt to imitate possible natural mechanisms is sounder than the instant resort to unnatural procedures such as dragging with brute force on the delivered head, though it must be admitted frankly that many cases come to this expedient. He would have more to say later about the place of head traction in this condition.

The clinical phenomena of broad shoulder dystocia

The patient is usually a mother of 3 or more children. Antenatally, a careful observer may have recognized that the child was unusually large, though this is notoriously difficult to judge.

In labour the initial presentation has been generally either occipito-lateral or so near to it as to make no material difference. Usually the head has negotiated the pelvic cavity without too much difficulty, though it may have been necessary (especially in the occasional primigravid case) to intervene in the second stage. In such circumstances, if manual rotation of an occipito-lateral or occipito-posterior position has been required, it has usually been rather difficult, and there has been some doubt of the complete correction of the child's body.

The delivery of the head with or without forceps may have been quite easy, but more commonly there has been a little difficulty in completing the extension of the head. The hairy scalp slides out with reluctance. When the forehead has appeared it is necessary to press back the perineum to deliver the face. Fat cheeks eventually emerge. A double chin has to be hooked over the posterior vulval commissure, to which it remains tightly opposed. Restitution seldom occurs spontaneously, for the head seems incapable of movement as a result of friction with the girdle of contact at the vulva. On the other hand, gentle manipulation of the head sometimes results in a sudden 90 degree restitution as the head adjusts itself without descent to the antero-posterior position of the shoulders.

Time passes. The child's face becomes suffused. It endeavours unsuccessfully to breathe. Abdominal efforts by the mother or by her attendants produce no advance, gentle head traction is equally unavailing.

Usually equanimity forsakes the attendants. They push, they pull. Alarm increases. Eventually

"By greater strength of muscle
Or by some infernal juggle"

the difficulty appears to be overcome, and the shoulders and trunk of a goodly child are delivered. The pallor of its body contrasts with the plum coloured cyanosis of the face, and the small quantity of freshly expelled meconium about the buttocks. It dawns upon the attendants that their anxiety was not ill-founded, the baby lies limp and voiceless, and only too often remains so despite all efforts at resuscitation.

Principles of management

Whatever may be the objections to making traction upon the neck of the child—and they are many—there is no doubt that as a first step it is safe and prudent to begin by making very gentle traction on the delivered head, drawing it gently backwards without forced rotation and without excessive angulation, at the same time exhorting the conscious patient to bear down. This is essentially a diagnostic procedure, for if the condition is one attributable merely to the friction of large shoulders in the oblique or transverse diameters, these simple measures will almost always produce a speedy advance. If the patient is anaesthetized fundal pressure should be made by an assistant synchronously with the traction. It is important to make the traction smooth and continuous and to avoid the application of sudden jerks. The duration of tractive effort should rarely exceed 4–5 seconds. One effort is enough. If it fails the attempt at delivery should be abandoned in favour of other methods.

The most profitable is undoubtedly to endeavour to imitate the postulated mechanism of rotation, to carry the bisacromial diameter towards the transverse diameter of the pelvis. Many persons have written in praise of this technique, which may be applied by abdominal manipulation of the anterior shoulder or by vaginal manipulation of the posterior one. For many editions de Lee's textbook has carried a fine illustration showing a bimanual technique. Woods (1943) restated the mechanical principles, and suggested that the rotation not only produced disimpaction but actually favoured descent of the foetal body as a bolt is made to progress through a nut by rotation with a screw driver. Løvset (1948) described a vaginal method whereby with the fingers placed in the posterior axillary fold of the posterior axilla he was able to achieve the necessary rotation.

In the experience of Professor Morris the vaginal methods are not easy. Indeed they appear much easier in an illustration than they are in life. The artist usually draws a sagittal section in which the hand of the accoucheur appears no larger than that which might be expected to belong to the foetus. The introduction of a fairly large hand is greatly obstructed by the close apposition of the mother's tissues to the base of the child's skull. Unless the hand is inserted with real caution and a superabundance of lubricant, much perineal damage may be caused. The lubricant then makes it difficult to grip any portion of the foetal body.

Professor Morris then described a manœuvre to overcome some of these difficulties by avoiding the introduction of the whole hand into the vagina. If it is to succeed, general anaesthesia is required and should be induced quickly if the patient has not yet been anaesthetized. This done, the posterior shoulder is located by recognizing the clavicle, which can usually be identified when a single finger is thrust deeply into soft tissues at the base of the neck. The posterior shoulder is then subjected to firm pressure with the tips of two fingers placed in the delto-pectoral triangle of the axillary wall of the foetus while an abdominal hand endeavours to manipulate the anterior shoulder in the opposite direction. It is not essential in every case to carry the rotation through an arc of 90 degrees. Indeed, once the bisacromial diameter has been dislodged from the conjugate diameter into something approximating to the oblique, it is worth while to try another gentle effort of traction on the head. The accoucheur is often delighted to find the

situation greatly altered for the better, and the delivery may be completed with surprising ease.

If this simplified procedure fails, then he preferred to pass the whole hand into the uterus and to bring down the posterior arm. This is a most effective procedure, and is followed by very easy delivery of the remainder of the child. So efficient is it that it may well be asked why it is not advised as an elective procedure. This was not advised since he believed that the forcing of the hand past the head and into and through the vagina is a grossly traumatic procedure liable to cause tears even in grandly multiparous patients, and the intra-uterine manipulations may result in uterine rupture.

There remains to be discussed the use of metal instruments. Traction on the axilla with a breech hook is effective, but the introduction of the instrument high into the birth canal is a highly dangerous procedure, and the damage which might result to the vessels and nerves of the axilla of a living child may well be imagined. In the dead and macerating infant there may be a place for this type of angling, but generally the corpse of the child can be extracted quite easily after the clavicles have been cut through with strong scissors.

The prevention of Erb Duchenne paralysis

There is no doubt that this is the principal danger to babies who survive the hazards of impacted shoulders. As an undergraduate he used to frequent infant welfare clinics a great deal, and saw rather a large number of cases which appeared to have arisen in this manner. Now it is by no means certain that the birth palsy referred to by the name of Erb Duchenne paralysis is invariably an uncomplicated lesion of the axon fibres leaving the cord by the 5th and 6th cervical motor roots. But the cases which he saw all appeared to exhibit signs of brachial plexus injury which persisted long after other causes of loss of power in the limb must have passed off. He considered it justifiable to lay down as a hypothesis that birth palsy is a brachial plexus lesion, and then to examine the circumstances in which the brachial plexus may be particularly liable to injury during traction on the head.

Adson (1922) did classical work on traction injuries of the plexus, using the method of experiment in adult cadavers. He found it very difficult to sever the fibres even with forces of many hundreds of pounds, but showed very interestingly, however, that a plexus which would withstand the gradual application of such a force might be readily torn if the same force were suddenly applied. The weakness of Adson's work, however, was that his criterion of damage was the naked eye appearance of tearing in the roots trunks or cords of the plexus, and that after the nerve bundles had been dissected free from the surrounding areolar tissue. It is quite possible that in life the owners of Adson's plexuses might well have had serious neurological signs as a result of injuries to individual axon fibres of a degree which could not show in naked eye studies: and further that the fixation of the greater part of the plexus as a result of its fascial attachments might render it more fragile when exposed to certain local strains than would be the case when the whole plexus was dissected free and able to slide or glide in response to such strains.

Recognizing these weaknesses, Professor Morris nevertheless decided some years ago to have a look at the brachial plexus in a few babies that came to autopsy to determine whether or not it was possible to recognize any procedure which greatly increased the tension on the plexus and especially on its upper trunk where the fifth and sixth cervical nerve bundles meet and mingle. Dr. F. A. Langley was good enough to dissect out some plexuses for him.

The first point elicited in the subsequent experiments was that simple traction upon the neck with the thoracic and cervical spine in the same axis appeared to have no effect whatever on the plexus, the structure of which remained quite lax, exhibiting a gentle curve from neck to axilla, with no suggestion of tension.

If, however, the head was tilted strongly towards one shoulder, the upper trunk of the brachial plexus on the opposite side at once became somewhat tight, and when to this lateral flexion there was added traction in the new axis of the cervical spine, the tension became quite severe.

If, now, as a preliminary to traction, the neck was

(*a*) Laterally flexed and

(*b*) Rotated so as to carry the child's chin away from the side on which the plexus was being studied, then traction produced the most extreme form of tension observed during the experiments.

It is perhaps claiming too much dignity for the investigations to classify them as experiments but, rough and ready as they were, Professor Morris felt inclined to draw certain conclusions from them.

(1) Traction on the head is least likely to injure the plexus when the cervical and thoracic portions of the child's spine are in the same straight line.

(2) Lateral flexion of the neck increases the risk of traction quite sharply.

(3) The addition of torsion of the neck to lateral flexion increases the danger further.

(4) Jerking is much more dangerous than smoothly applied traction.

He thought that these cautionary precepts should be kept continuously in mind in making traction on the head of the child, even when the situation is something short of the complete impaction which has been the principal topic of the paper. He advised against excessive lateral flexion of the neck in all cases. The idea dies hard that by swinging the child's head far back we can apply traction more effectively in the axis of the pelvic brim. In fact the main line of transmission of the force is the vertebral column, and the only effect of lateral flexion of the neck is to ensure that less of the force is transmitted by the spine and more by the fasciae, the brachial plexus, and the skin. The attempt to facilitate internal rotation of the trunk by forcible external rotation of the head may be very dangerous if it leads to subsequent traction being made on a twisted neck, a result by no means unusual.

References

Adson, A. W. (1922): *Surg. Gynec. Obstet.*, **34**, 351.
Løvset, J. (1948): *Nord. Med.*, **38**, 1127.
Woods, C. E. (1943): *Amer. J. Obstet. Gynec.*, **45**, 796.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

November 1954

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Liverpool on Friday, 19th November, 1954, with the President, Dr. K. V. Bailey, in the Chair.

Mr. P. C. Barkla read a paper on

Hydatidiform Mole and Chorionepithelioma

(This article appears on page 239 of this issue)

Discussion

Mr. C. H. Walsh had always thought that chorion-epithelioma could develop only from trophoblast, although that tissue might lie dormant for a long time. He had never seen hydatidiform mole recurring in the same patient but Mr. Barkla assured him that such occurrences had been reported.

Mr. F. Stabler reminded the Society that one of its members, Mr. F. J. Burke, had described a type of lesion which lay between simple hydatidiform mole and frank chorionepithelioma, which was characterized by local malignancy only, and which might lie dormant for years. The present case might come into this group.

Dr. R. E. Rewell emphasized the possible pitfalls in the pathological diagnosis of chorionepithelioma and Miss Eleanor Mills supported this point, citing 2 illustrative cases.

Professor W. I. C. Morris said it was a general truism that any cancer might lie dormant for years before breaking loose and killing the patient. He described 3 cases which illustrated that when simple hydatid mole was diagnosed chorionepithelioma might already be present in the uterus.

Professor T. N. A. Jeffcoate read a short note on

Salpingectomy or Salpingo-oöphorectomy?

(This article appears on page 214 of this issue)

Discussion

Mr. R. M. Corbet warned that in dealing with ectopic pregnancy it was important to cover over the cut end of the tubal stump. Twice within a short time he had seen a further pregnancy in a tubal stump, and that when the ipsolateral ovary had been removed.

Professor T. N. A. Jeffcoate read a short note on

Vertebral Venous Drainage of the Pelvis

(This article appears on page 244 of this issue)

Mr. S. Bender read a short paper on

Fertility After Tubal Pregnancy

Mr. Bender had been able to follow up 256 out of 295 women operated on for tubal pregnancy 2 to 7 years previously. Within the time of this limited follow-up, 44 per cent of these women conceived again but only 32 per cent produced a living baby. If a woman who had had a tubal pregnancy conceived again her chance of a further ectopic gestation was increased almost fifty-fold because the recurrence rate was 16 per cent.

In relation to Professor Jeffcoate's note, it was interesting to note that among 183 women treated by salpingectomy the conception rate was 42 per cent, whereas it was 52 per cent in 48 women in whom salpingo-oöphorectomy had been performed.

Mr. Bender showed the poor results that attended salpingostomy carried out at the same time for blockage of the non-pregnant tube. Salpingostomy on the affected tube, an operation which could probably be performed more often with advantage, was more likely to be followed by another conception. Finally, thorough peritoneal toilet and prophylactic post-operative chemotherapy might diminish the frequency with which the remaining tube became blocked and therefore increase the subsequent conception rate.

Mr. R. F. Lawrence read a paper on

The Rural Scene Surveyed, an Obstetrical Review

(This article appears on page 249 of this issue)

Discussion

The President congratulated Mr. Lawrence on the quality and content of his paper. He considered the maternal mortality rate commendably low in view of the high toxaemia rate.

Mr. S. B. Herd considered that this review raised the question of whether students were being taught so as to be prepared for practice in remote areas.

Professor A. M. Claye thought that in general better results might have been expected in view of the high proportion of healthy young primigravidae. He wanted to know whether Mr. Lawrence thought he would be better off with more hospital beds. He was answered in the affirmative, the speaker pointing out that, as he was the sole consultant in the area and his medical staff comprised merely 1 registrar and 2 general practitioner clinical assistants, it was more economic of time for the patients to come to the maternity units than for him to have to travel far and wide. In answer to Mr. A. A. Gemmell, who also stressed the importance of the socio-medical side of this survey, Mr. Lawrence said that his ambulance service was generally satisfactory, although occasionally difficulty arose over the transport of patients from other administrative areas.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

December 1954

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Manchester on Friday, 17th December, 1954.

Dr. K. Vernon Bailey delivered his Presidential Address entitled

Soliloquy

Dr. Bailey first remarked how interesting it had been to be President, and how much less disconcerting than he had imagined. Perhaps this was because one envisaged the

Society collectively and tended to acquire a sort of parental interest in its newer members—those men and women who had joined since the end of the war and largely since the appointed day, who had emerged as a result of yet another social revolution and whose efforts, sacrifices and outlook, whilst analogous to the old order, bore some contrasts to it.

For his Presidential Address therefore he would not present an historical or biographic essay, but something in a lighter vein—a few reflections and meditations concerning their own position as Consultants and potential Consultants in their specialty.

Broadly speaking he saw three main classifications—(i) the older Senior Consultant of the pre-N.H.S. era who controlled a Unit and was referred to euphemistically as "established"; (ii) the young Consultant, come to maturity and authority under the N.H.S.; and (iii) the Senior Registrars and Registrars who were battering at the walls of this Consultant State with all the weapons of experience at their command.

These last two groups had greatly increased in recent years, had changed the picture representing specialization to some extent, and incidentally had greatly increased (and naturally improved!) the membership of this Society. He found himself interested in them and their future, in the hazards peculiar to them, in the impact they would make upon a public attuned to Universal Welfare and in the impact they would make upon the specialty itself. During this year of presidency he had pondered upon considerations which might influence their professional lives and had soliloquized upon the contrasts between then and now and also upon the conditions and standards which appertained in other countries.

With regard to the "Old days" a few pictures remained. There were four generations of gynaecologists each of whose phases of activity, whilst overlapping, was nevertheless apparent over a number of years. There was firstly a generation which had gone before, but whose reputation still lingered, containing Lloyd Roberts and Jap Sinclair, Carlton Oldfield, Rankin Lyle, and Briggs—one might say a "pioneering generation". Next a senior generation nearing the end of its active phase—including Donald, Fothergill, Clifford, Gemmell (Senior), Gough (Senior), and Miles Phillips for whom they had had the honour to work. They must have felt the early satisfaction of clinical fulfilment—an "establishing generation". Thirdly there was a generation of Assistant Honoraries—which included Sir W. F. Shaw, Lacey and Dougal—which inherited early clinical and scientific legacies and was concerned in the production of many changes and advancements, and which thrived in an era of sound national economy. He felt that this was indeed the Golden Age in their specialty, and one member of it he was glad to see here today—Sir William Fletcher Shaw, the fruits of whose labours had become even more apparent under the conditions now prevailing; in fact, some of them might be said to be present that afternoon!

The fourth generation contained himself and his colleagues in whose time interesting changes had occurred. They had begun under the old regime with no income to speak of and not much assistance and had emerged into the new one, in which a controlling State had seen to it that there had been an increase in the latter! Nevertheless, there had been the compensation of high hopes in the old system of control, penury, and extreme uncertainty, when there was nothing to lose but time. His had been the "generation of transition" which had inherited and carried on an established tradition. And now there had appeared a fifth generation of young Consultants—which had changed the old order of things. The two main corollaries which emerged from this change—apart altogether from the question of the service to the public—were concerned with firstly the difficulties and even injustices on the road to the consultant state, and secondly the possible change in the academic and scientific outlook which might overtake these consultants of the future. The former concerned the registrars, too many of whom after many years of effort would fail to qualify and here his thoughts became a little sombre.

To begin with, he had never cared for a too avid control of the profession. Dr. Bailey then quoted from official pronouncements in 1952 and 1954 regarding the prospects of senior registrars the effect of which was that in one breath responsibility was effaced but consolation was offered, and meanwhile the bottleneck became more pronounced. "The Ministry has made it quite clear that there is no possibility of any substantial increase in the number of Consultant posts, and over the next 10 years there would inevitably be a heavy wastage of Senior Registrars and Registrars." However, he still maintained that these Registrars of long training should be allowed to qualify as consultants. It was not they who had proved unsatisfactory but the machine, and something should be done even if it meant making two appointments where there was now one; for what else offered itself to these highly qualified and probably married medical men and women of over 30 who found themselves in this position because of a misconception which was not of their originating?

What other opportunities were there for them?

With the probable exception of certain provinces of Canada, there was little prospect for a British potential Consultant in the Commonwealth Countries today.

There were only six of the territories served by the Colonial Medical Service with Obstetrical and Gynaecological Specialists. As for the Armed Services, in the R.A.M.C. there were at present only 10 appointments suitable for Officers of Consultant status. Although the clinical scope in these posts was sufficient to provide a full and satisfying professional life, there was not the same wealth of clinical material as passed through a large civilian hospital. The problem before the Registrar was today a difficult one and the solution was becoming progressively limited.

On the other hand, the young man who had acquired Consultant status and a post that went with it was a fortunate member of our Society today. He might be brilliant, and have worked long and hard and had his moments of anxiety. Nevertheless, he had emerged from an almost equally brilliant and large field—and at the right time—because the future decade would not hold the prizes of the one just past.

He was interested, said Dr. Bailey, in the young Consultants of the post-war era and, if he were to worry about them at all, it would only be in relation to the continued and progressive advance of our specialty in this country, and the maintenance here of the initiative in the higher clinical and scientific spheres in those years which would follow the passing of his own generation. He would worry, for instance, if they failed to look beyond the relatively limited spheres of their own particular unit—if they tended to become Obstetrical and Gynaecological technicians within their regions—if they continued to rest content with their particular posts, and if they failed to maintain continued contact with learned Societies, the Teaching Hospitals and the Universities. They were doubly fortunate in so far as not only in this country but internationally their position was unique—affording as it did the facilities for the furtherance of discovery in our specialty, by allowing that full control which could result in freedom of endeavour. He could remember men being assistants to the chief of a unit on the Continent for 15 years and more. Things might have improved since then, but in visiting the more modernized North European Countries since the war he had noted that a degree of state control with full-time staff had tended to supervene.

Dr. Bailey then described the situation regarding training and staffing as he had seen it in Denmark, Holland and Western Germany, where state control was close and where candidates greatly out-numbered vacancies. In Spain, which he had visited in 1952, he had found a time of transition from old hospitals to new, and a high level of work despite facilities not being modern by our standards. Perhaps a shortage of state funds was the difficulty. Chief clinics like those at Barcelona and Madrid were under the strict control of a Director of the Staff. The Staff, however, were numerous and a minor degree of private practice was permissible among them. The Spanish not being allowed beyond their own borders must be restricted to some extent in their professional outlook.

In Rome a mixed and partly state-aided system of hospitals operated. The system for specialization was complex and restricted all but the lion-hearted, for applicants far outnumbered vacancies.

In Athens he had met Professor Louros who succeeded his father in the Chair of Obstetrics and Gynaecology in Athens. Prior to this he was Professor in Berlin where he was trained (and incidentally when the Germans occupied Athens in the last War he was sent to a concentration camp for failing to collaborate as expected). The system for specialists in training was, following 7 years to qualify in medicine, to take 1 year in General Surgery followed by 3 years in Obstetrics and Gynaecology, all without pay. Thereafter application could be made for an assistantship, after 3 years of which one could qualify by examination for the status of Specialist. The system for admission of patients to hospital according to their means was interesting and rigid: 1st Class or Private Patients occupied either a single or double room and paid for accommodation and fees from their own capital; 2nd Class patients occupied 4-bedded wards and paid part accommodation from a form of Medical Insurance personally entered into; 3rd Class patients occupied 6- and 8-bedded wards, the maintenance costs of which were drawn from their Industrial Insurance Scheme; 4th Class patients were the very poor, paid for by the state fund.

This system was a realistic method of assessment and one calculated to enable the people to appreciate their Medical Services!

In the New Alexandra Hospital, Professor Louros had built a special Guest Suite to house some 10 Consultants and their wives with all comfort, with the object of instituting periodical small personal congresses in which the Consultants would stay for some days as his guests and engage in scientific and clinical discussions.

Dr. Bailey then described his visits to Rhodes, Cyprus and Istanbul. In Turkey doctors could specialize by attending for 4 years with a recognized Obstetrical and Gynaecological Unit. After 1 year general surgery and 3 years obstetrics and gynaecology, a thesis was written and, if this was accepted, the applicant took an examination and was assessed by a jury before becoming a Specialist. Turkey, therefore, conformed in general to the pattern of the other Southern European States—where there was no complete governmental control and no Welfare State, but where there was a professorial oligarchy, on the one hand, and a free market in the private clinics, on the other. The road was made very hard, but there was a means of existence at the end of it for those who might fail to fulfil their own early hopes and desires. The outlet for private practice did not depend so much upon hospital appointments, although the standard must suffer commensurately. The disciplinary control and atmosphere in which the applicant to specialize grew up under the Director of the Clinic must have a lasting effect and make a lasting impression upon his mind and outlook which should stand him in good stead during his future career—that is if the Director himself was a good man.

At this juncture Dr. Bailey showed a film illustrating his travels.

Dr. Bailey concluded by saying that Obstetrics and Gynaecology seemed to continue the even tenure of its way, without spectacular changes, in those countries of the older civilization. Perhaps the dignity of medicine, possibly to the detriment of the mass of the public, was upheld and maintained by the Hospital System which prevailed there where the successful Gynaecologist need have no hospital appointment. He wondered whether time and western influence would affect these things—for better or worse. If their young men could visit us, they must wonder at the vast wealth which goes into our ordered medical state, and it would behove us therefore in the years to come, to justify our inheritance by continued leadership. He supposed, as Homer said, "These things must remain on the knees of the gods".

Thanks were recorded to the President for his Address by Mr. A. A. Gemmell (Liverpool), Sir William Fletcher Shaw (Manchester), Mr. H. J. Malkin (Sheffield), Professor A. M. Claye (Leeds), and Professor E. Farquhar Murray (Newcastle).

BOOK REVIEWS

"Chronic Iliac Pain in Women." By H. B. ATLEE, M.D., F.R.C.S., F.I.C.S. Pp. 65, 6 figures. Charles C. Thomas, Springfield, Illinois, and Blackwell Scientific Publications, Oxford, 1954. Price 18*s*.

DR. ATLEE, in a short book on chronic iliac pain in women, lists the various diagnoses which have been made and discusses each in one of the following nine sections: chronic appendicitis; "adhesion"; painful ovary and/or Fallopian tube; "cyst" of the ovary; such uterine conditions as prolapse, retroversion, tears and erosions of the cervix, and chronic cervicitis; painful conditions of the ureter; abdominal wall neuralgia due to neuritis of the cutaneous branches of one of the lower dorsal or upper lumbar spinal nerves; the caecal syndrome, due to irritation or spasm of the caecum; and iliac pain as a manifestation of a neurosis.

The author's main criticism of the treatment of right-sided chronic iliac pain is that the principal diagnostic procedure is the laparotomy itself. He advocates the most complete study of the patient, which should include radiological, urological and psychiatric investigations, before any operation is considered. He states that it may be "laid down almost as an axiom that a chronic right-sided pain that is constantly present is not due to appendicitis" and that to make such a diagnosis "would therefore seem not only to be stupid but sinful".

Dr. Atlee does not think that chronic iliac pain often arises in the ovary, Fallopian tube, uterus, or cervix uteri or that it is likely to be caused by adhesions. He stresses the importance of excluding a urological cause for the pain but inclines to the view that caecal pain, for which he recommends a bland diet, and "psychic" pain are the commonest cause of this type of pain in women.

This book is published in Canada where presumably much of the pelvic surgery is undertaken by general surgeons. Notwithstanding the fact that the author seems unaware of the possibility of iliac fossa pain being caused by the inharmonious activity of pelvic sympathetic nerves, this is a very valuable little book, challengingly written by a transparently honest and experienced clinician. Unfortunately it is not likely to fall into the right hands in this country and is more liable to be read by the converted than the unconverted. Its price, moreover, will tend to limit its circulation.

"Gynaecology." By DOUGLAS H. MACLEOD, M.S., F.R.C.P., F.R.C.S., F.R.C.O.G., and CHARLES D. READ, M.B., F.R.C.S., F.R.A.C.S., F.R.C.O.G. Fifth Edition. Pp. xii+864. 551 illustrations, 27 in colour. J. & A. Churchill, Ltd., London, 1955. Price 80*s*.

THIS well-known textbook has had a somewhat chequered career. Appearing first in 1916 under the authorship of Eden and Lockyer it at once established itself as the most complete and authoritative statement of British gynaecological practice at that time. Its popularity was evident by its passing through three editions in twelve years under the same authors. The fourth edition appeared after an interval of seven years under the editorship of Beckwith Whitehouse. Thereafter it fell by the way for the long period of twenty years and it must have seemed to many that with the death of Sir Beckwith Whitehouse the book was fated to suffer a natural demise. We may safely surmise that this long gap in publication was not due to any loss of interest on the part of the publishers. Whatever the cause of the delay the medical profession and gynaecologists and their students in particular will welcome this long overdue edition.

To some it will revive memories of their early career when "Eden and Lockyer" was a familiar occupant of their shelves and to some the arrival of the new volume will revive the genial memory of Dr. Watts Eden and of Dr. Cuthbert Lockyer, to whom in his retirement it must mark another milestone in his long life.

The present authors have wisely retained much of the text, especially on the clinical side, which has retained its relevance to the present day. Elsewhere they have carried out a complete overhaul. In this they have had the collaboration of Mr. James Snyder, who has written an excellent chapter on Anatomy, and of Dr. Russell Fraser, who, as a physician long identified with the problems of Endocrinology, has written with authority some of the sections dealing with Physiology.

The volume in general deserves high praise. The arrangement is good, the style is simple and direct and, whilst, where the occasion arises, discussing alternative views, it leans towards that measure of dogmatism that is desirable in a good textbook. The illustrations are in general of a high order and those dealing with pathology are in particular worthy of special praise as is natural in a book having access to the unrivalled material of the Chelsea Hospital for Women.

As we would expect from the standing of the editors, the chapters dealing with the clinical and therapeutic and operative sides are throughout excellent. In this connexion we would specially pick out the chapters on Displacements, Tumours, Endometriosis and Operations.

We have had here and there our disappointments in reading the text. There is rather a cursory reference to the new and apparently well-established Stein-Leventhal Syndrome. Its frequent association with masculinization is not mentioned and the Syndrome does not appear in the Index. Then, in view of the fact that probably very few pathologists now believe that the amount of elastic tissue in the uterus has any special bearing on "Sub-involution", it seems rather out of place to retain from the previous editions the florid illustrations occupying three large plates. The strong preference for radical

surgery as against X-rays and radium for the establishment of an artificial menopause in cases of "functional" uterine haemorrhage will shock many readers who believe that non-operative measures should have a firmer claim than the editors are prepared to admit. Having regard to its importance to pathologist and clinician alike there is very scant reference to carcinoma *in situ* and we should have liked to see a more adequate description of the technique and a more adequate discussion of the place and value of the vaginal and cervical smear in the detection of early genital carcinoma.

For a volume so happily resuscitated we may safely predict a new edition in the early future; this will provide the opportunity to deal with any valid criticisms. Meanwhile we congratulate publishers and editors alike on a worthy contribution to British medical textbooks.

FOURTEENTH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY, OXFORD

27TH TO 30TH JULY, 1955

President:

Professor J. Chassar Moir, F.R.C.O.G.

Honorary Secretaries:

J. Stallworthy, F.R.C.O.G., W. Hawksworth, F.R.C.O.G.

THE 14th British Congress of Obstetrics and Gynaecology will be held in Oxford on 27th–30th July, 1955.

Applications for membership are still being received and those desirous of attending the Congress are advised to apply without delay to the Honorary Secretaries, 14th British Congress of Obstetrics and Gynaecology, The Radcliffe Infirmary, Oxford, from whom full particulars may be obtained.

SECOND WORLD CONGRESS ON FERTILITY AND STERILITY

THIS Congress, sponsored by The International Fertility Association, will be held in Naples, Italy, from 18th–26th May, 1956.

Invitations are extended to those who may wish to contribute scientific papers.

Those interested should apply to Dr. G. I. M. Swyer, University College Hospital, Huntley Street, London, W.C.1.

REVIEW OF CURRENT LITERATURE

CONTENTS

	REF.
PHYSIOLOGY	64
PREGNANCY	66
LABOUR	70
LACTATION	78
INFANT	80
GYNAECOLOGY	82

PHYSIOLOGY

64. **Plasma-17-Hydroxycorticosteroids in Pregnancy.**
By R. I. S. Bayliss, J. C. McC. Browne, B. P. Pound and A. W. Steinbeck. *Lancet*, **1**, 62–64. Jan. 8, 1955. 2 tables. 2 figs. 31 refs.

Although there is evidence of an increased urinary excretion of certain adrenocortical steroids such as glucocorticoids during pregnancy, no increase in the excretion of androgenic or 17-ketosteroids has been observed by a number of workers. The authors therefore investigated the plasma of 30 women who underwent a normal pregnancy. Samples of blood were taken throughout pregnancy at monthly intervals and in 15 cases blood was also collected from the umbilical cord at the time of delivery. The concentration of 17-hydroxycorticosteroids in the plasma was estimated by a modification of the method of Nelson and Samuels. They found that the level was 10 μg per 100 ml. at the third month of pregnancy and the same as the mean value for non-pregnant women. Thereafter the level rises steadily to delivery. Post-partum the level gradually falls to normal by the eighth day. The authors believe that the site of origin of the 17-hydroxycorticosteroid material in pregnancy is the maternal adrenal glands and that the corticotrophic hormone responsible could come from either the maternal pituitary or the placenta.

H. H. Fouracre Barns

65. **The Influence of Female Sex Hormones on the Blood Cholinesterase and Acetylcholinesterase.** (Der Einfluss der weiblichen Sexualhormone auf die Cholinesterase und Acetylcholinesterase.)
By H. Burger. *Arch. Gynäk.*, **185**, 347–358. Dec. 1954. 11 graphs. 32 refs.

Experiments to determine the influence of female sex hormones on specific and unspecific cholinesterase were carried out on the blood of 9 women (6 of whom had ovulatory and 3 anovulatory cycles) and several men (number not stated) who were given 1 mg. follicular hormone or 10 mg. progesterone intramuscularly.

It appeared that serum cholinesterase activity was in general higher in men than in women but these differences were of no statistical significance. Similarly, no significant differences were found in erythrocyte acetylcholinesterase of males and females. Neither serum cholinesterase nor erythrocyte acetylcholinesterase showed any variations during the menstrual cycle. Intramuscular injection of 1 mg. of follicular hormone into males was followed by a more or less marked diminution of serum cholinesterase as well as erythrocyte cholinesterase values with a maximum depression at 8 hours. Injection of 10 mg. of progesterone had no effects within 24 hours.

In vitro experiments with follicular hormone, progesterone, cholesterol and desoxycorticosterone failed to show any influences on enzymatic activity.

These negative results indicate that the well-known changes in vegetative tonus occurring during the menstrual cycle are not correlated with any changes in cholinesterase.

E. Wachtel

PREGNANCY

66. **Control of Cross-infection by Means of an Antiseptic Hand Cream.**
By J. Murray and R. M. Calman. *Brit. med. J.*, **1**, 81–83. Jan. 8, 1955. 5 tables. 7 refs.

Pyogenic staphylococci and streptococci, nowadays the most common and important organisms encountered

in maternity hospitals, circulate among the personnel and throughout the buildings. The reservoir of these organisms is the nose (60 per cent of nurses at Queen Charlotte's Maternity Hospital, London, were found to carry pyogenic staphylococci in their noses) and the main method of transfer is thought to be by way of the hands.

The cycle of transfer of organisms can be interrupted by treating the hands of personnel with antiseptic cream.

Investigating a group of antiseptics the authors were struck by the high antibacterial properties of a new compound 10,040 [formula given]. One per cent of this substance was incorporated in a special emollient which would not inhibit the antiseptic and yet at the same time would be cosmetically attractive and therefore freely used by the staff.

In the laboratory, using a fingerstall technique, the writers, having shown that the number of colonies of "resident organisms" recoverable from adjacent fingers, did not vary very much, found that very few colonies could be recovered from fingers treated with the antiseptic, compared with the number recovered from untreated fingers of the same hand.

In subsequent tests, fingers were deliberately contaminated with a strain of *Bacterium coli*. Very few organisms could be transferred by "creamed" fingers as compared with control untreated fingers.

When these investigations were completed, tubes of the antiseptic cream ("Hibitane") were placed beside each wash basin in wards and nurseries, and the staff were encouraged to rub 1·5 to 2 g. of the cream on to their hands as often as possible after washing between cases.

No case of idiosyncrasy to the antiseptic has occurred during the 18-months clinical trial. During this time the number of staphylococcal infections in the hospital has been reduced and there have been no serious infections. Those infections which did occur were scattered throughout the hospital and no longer appeared in groups in particular wards. Use of the cream is recommended in all departments where cross infection is likely to occur.

R. W. Grayburn

67. The Fertility of Elderly Primiparae after Caesarean Section. (Über die Fertilität der schnittentundenen alten Erstgebärenden.)

By H. HIRVONEN, K. NIEMINEVA and L. HIRVONEN. *Acta obstet. gynec. scand.*, **33**, 384–394. 1954. 7 figs. 13 refs.

One out of 5 primigravidae of over 30 years of age is delivered by Caesarean section at the Obstetric Clinics of Helsinki. The subsequent deliveries of 356 such women who had undergone Caesarean section between 1925 and 1950 were recorded according to the entries of births in parish and civil registers.

It was found that the fertility of these women was considerably lower than the average fertility of married women in Finland. However, the prospects of further pregnancies in women delivered by Caesarean section of their first babies after the age of 30 was found to depend on the same factors as in other parturients; the most important of these factors were the age at the first section and the duration of childless marriage before their first conception, whereas the fact that they were delivered by Caesarean section did not appear to be of significance.

N. Alders

68. The Significance of the Placenta in "Obstetrical Mortality".

By C. J. KLOOSTERMAN and B. L. HUIDEKEPER. *Gynaecologia, Basel*, **138**, 529–550. Nov. 1954. 10 refs. [In English.]

This is a report of an investigation of 2,000 placentas with reference to the ratio of placental weight to foetal weight and to the presence of infarction. It was found that the placenta hardened in formalin could be better examined for the presence of infarcts and haemorrhages than one preserved in a refrigerator and that the hardened placenta could be more easily cut in slices. A classification of infarction was devised, dividing placentas into four groups, group 0 with no infarction and groups 1 to 3 with little to considerable infarction. In the total series, infarction was found in over 40 per cent of placentas. The weight ratio placenta to child becomes progressively smaller with the duration of pregnancy. Even the smallest degree of placental infarction influences the placenta/child weight ratio and this suggests that the placenta has only a very small functional reserve as the ratio is changed at the expense of the child. During pregnancy the placenta is fully active and is only capable of a slight degree of compensation when partly inactivated by degeneration. Therefore infarction of the placenta is a serious matter as it is probable that a fairly severe degree of infarction, which always seriously impedes intra-uterine development, may lead to death of the child. This is shown in the foetal mortality in this series. In cases where the cause of death was known the degree of infarction was significantly lower than in the group labelled "cause unknown". This confirms the opinion that infarction is the cause, and not the result of foetal death. Infarction is especially dangerous in small placentas.

Male foetuses tend to have a higher birth weight than female foetuses and it thus follows that male babies demand more of their placentas than females. This does no harm if the total "male ovum" is larger in the same proportion but if this is not the case the male foetus has a more unfavourable placental weight coefficient than the female foetus. This offers an explanation of the known fact that the intra-uterine mortality of boys is markedly higher than that of girls.

A study of toxaemic placentas showed that toxaemia does promote infarction of the placenta yet, in cases of severe toxaemia, placentas without any infarction may be observed and placentas showing marked infarction may be seen in cases without the slightest evidence of toxaemia. Toxaemia does not have an unfavourable effect on the growth of the placenta. In fact the placenta is often heavier and it is probable that the liability to toxaemia is directly proportional to the amount of functioning placental tissue. Toxaemia does endanger the child, but only before birth.

Vascular sclerosis, in the small numbers available in the series, has an unfavourable effect on the growth of

the placenta. The influence of this condition on foetal death rate appeared to be very marked.

The fact that firstborn children tend to weigh less at birth than other children is confirmed in this series. Primiparity has an unfavourable effect on the placenta in that there is somewhat more infarction together with smaller placental weight but there must be a third, so far undiscovered factor, in primigravidae. It is believed that vascularization of the uterus plays a part.

In conclusion it is established that the placenta is of great importance in connexion with intra-uterine death.

[This important piece of work has been fully abstracted. There are many interesting points in it, but one of the most important is the emphasis thrown on the need for careful study and investigation of the placenta in all cases and particularly in cases of apparently unexplained intra-uterine foetal death.] *Josephine Barnes*

69. **Anaemia of Pregnancy Treated with Intramuscular Iron.**

By J. M. Scott and A. D. T. Govan. *Brit. med. J.*, **2**, 1257–1259. Nov. 27, 1954. 4 figs. 11 refs.

The results are reported of treating 50 pregnant women who suffered from iron deficiency anaemia with a new preparation "imferon", given intramuscularly. All had haemoglobin levels less than 10 g. per cent (68 per cent on the Haldane scale) and only 14 women showed a level over 8 g. per cent. Investigations proved that the anaemia was always primarily of microcytic, hypochromic type. Most cases received doses representing 250 mg. of elemental iron twice weekly, some of the earlier ones being given a smaller daily dose. As each millilitre of solution contains 50 mg., large volume injections were not a problem and there were no reactions, either local or general, provided the needle was inserted really deeply into the gluteal muscles. If the injection is too superficial, there is risk of superficial staining and poor absorption.

Progress was followed by regular haemoglobin, haematocrit, reticulocyte and serum iron readings. An average weekly dose of 500 mg. produced an increase of just over 1 g., or 6 per cent, in the haemoglobin level, a result comparable with those obtained by the use of intravenous injections of saccharated oxide of iron. There may be some delay in response with either method of therapy, but by the second week all patients in this series showed similar haemoglobin increases.

Doreen Daley

LABOUR

70. **The Application of Certain Principles of Physics to the Physiology of Delivery.**

By F. H. Howard. *West. J. Surg. Obstet. Gynec.*, **62**, 607–609. Dec. 1954. 6 refs.

The author uses the squatting position for delivery and argues that the laws of gravity and mechanical action and the principle of the Cartesian diver provide evidence that this position is less traumatic to the foetal brain than is delivery in the horizontal positions.

[The arguments as presented are not convincing.]

D. C. A. Bevis

71. **Management of Labour in Reference to Prevention of Perinatal Mortality.**

By G. E. Judd. *J. Amer. med. Ass.*, **156**, 1474–1480. Dec. 18, 1954. 18 refs.

An early estimation of the general factors involved during labour leads to proper planning and is the first step towards promoting foetal salvage. Support for the foetus can be provided by fluids given parenterally, by oxygen, and by the use of antibiotics to prevent foetal infection. Vitamin K is of doubtful value but at least it eliminates any subsequent prothrombinopenia. The intravenous Pitocin drip may be of value in inertia but extreme vigilance is necessary when it is used. Maternal factors such as age, gravidity, and previous history influence foetal loss, and evaluation of the foetal risk in complicated presentations should help to determine the type of delivery. Caesarean section may be done for many foetal indications, but recent reports suggest that a 1 per cent foetal loss must be accepted from the operation alone. For breech delivery with suitable planning in expert hands there should be no greater foetal risk than in cephalic presentations.

Management of premature labour calls for reduction in medication and anaesthesia. Cord blood should always be given to the baby by "stripping". Warmth and early oxygenation are very important and the procedure for resuscitation recommended by the author is as follows: a tracheal catheter, having freed the trachea of all fluid, is connected by a cannula of 2 mm. bore to a soft anaesthetic bag filled with humid oxygen. The nurse alternately compresses and relaxes the bag at a rate of 20 to 30 times per minute. This method has given excellent results, and intratracheal pressure up to 50 cm. of water has not caused lung damage.

D. W. James

72. **Delivery and its Relationship to Premature Rupture of the Membranes.** (El parto en su relación con la rotura prematura de las membranas ovulares.)

By R. A. Votta. *Obstet. Ginec. Lat.-amer.*, **12**, 234–240. June 1954. 21 refs.

A survey of the incidence of rupture of the foetal membranes before the onset of labour and the effects on the subsequent confinement are reported by the author. Of 1,522 deliveries in 1952 in a Buenos Aires maternity hospital, 225 (14·7 per cent) patients experienced rupture of the membranes before perceiving the onset of the uterine contractions of labour.

Analyzing the statistics, the author states that the incidence of this occurrence in primigravidae and multiparae was almost equal—114 and 111 respectively. In both groups the age factor showed that the highest percentage number occurred after the age of 34 years.

The onset of labour and its duration did not appear to be longer than usual. In 90 per cent of cases, labour began within 24 hours, and in 192 patients spontaneous delivery occurred: both stages of labour were shorter in duration than the average, regardless of parity.

Twenty-seven cases (12 per cent), however, required operative delivery, and the third stage of labour was complicated in 53 patients. Of the latter, 6 required

manual removal of the placenta, and there were 47 instances of post-partum haemorrhage.

The author concludes that in some cases painless uterine contractions are present before rupture of the membranes, thus accounting for the apparent shortening of the first stage of labour in the cases under review, but nevertheless he maintains that rupture of the membranes before the onset of labour presents a different phenomenon in uterine action from those cases in which the membranes rupture at a late stage.

John F. Foulkes

73. **The Use of Hydergine in Obstetrics.**

By P. B. PERCHESON and J. J. CARROLL. *Canad. med. Ass. J.*, **71**, 588–594. Dec. 1954. 1 table. 24 refs.

A review is made of 110 patients to whom Hydergine was administered in the presence of prolonged or arrested first stage of labour. The clinical picture most prominent was that of an emotionally unstable patient whose uterine contractions were of poor quality and character, with slow dilatation of the cervix. The drug was given when the cervix was 6 cm. or more dilated and was used in various dilutions, from one ampoule (0·3 mg.) in 5 ml. of sterile water to one ampoule (0·3 mg.) in 1,000 ml. of 5 per cent glucose solution.

In 70 patients (64 per cent of the series) the cervix became fully dilated within 20 minutes. Four-fifths of this group showed evidence of emotional overactivity. In 7 patients the presenting part was in the occiput posterior position. In the remaining 40 patients (36 per cent of the series) the cervix dilated fully within one hour in 21 patients, the other 19 patients requiring 80 minutes to 5 hours. Two-thirds of this group showed no evidence of emotional overactivity. In 10 patients the presenting part was in the occiput posterior position, and in 4 patients there was evidence of cephalo-pelvic disproportion. No foetal nor maternal deaths were ascribable to Hydergine, nor was any appreciable effect on the maternal blood pressure observed. In 4 cases the foetal heart sounds slowed to between 80 and 90 beats per minute, and in one case contractions of the uterus resembled a spasm for the duration of two pains.

The authors were impressed by the relative safety of Hydergine as compared to dihydroergotamine or pitocin. The drug proved to be of unquestionable value in cases of marked emotional instability and arrested labour, with a cervix dilated to at least 6 cm. The dilution of one ampoule (0·3 mg.) in 500 ml. of 5 per cent glucose solution by intravenous infusion was recommended. Definite evidence of cephalo-pelvic disproportion was considered a contra-indication to Hydergine therapy.

Otto Schmidt

74. **The Challenge of Dystocia.**

By B. J. HANLEY. *J. Amer. med. Ass.*, **156**, 935–937. Nov. 6, 1954.

In 1948 the author and Dr. J. C. McDermott devised the Hanley-McDermott pelvimeter for measuring the anterior pelvic depth. The instrument has a fixed bar 8 cm. in length with finger loops at each end. One end of a caliper is fixed at the midpoint of this bar and the other end is movable. The bar is inserted at a point where the divergence of the pubic rami reaches 8 cm. and the tip of the movable arm of the caliper is brought down on the upper border of the symphysis. The anterior pelvic depth is given on the scale. The incidence of midpelvic and outlet dystocia increases with the lengthening of this measurement. The reasons for this based upon the different mechanisms of labour are explained in detail. When the anterior pelvic depth measures 7 to 9 cm. no midpelvic or outlet dystocia should be expected. When it measures from 9 to 10·5 cm. minor problems will be encountered, and above 10·5 cm. the bony resistance is markedly increased. Above 11·5 cm. abdominal delivery is highly probable unless the foetus is extremely small.

Six years experience with this pelvimeter in 4,199 private patients has shown it to be of great value in anticipating this type of dystocia, and the author relies more upon the information given by this pelvimeter than upon radiological measurements except when the pelvis is asymmetrical.

D. W. James

75. **Dystocia Caused by Fetal Intracranial Teratoma.**

By J. A. WAGNER, L. H. DOUGLASS and V. T. SLAGER. *Obstet. Gynec.*, **6**, 647–652. Dec. 1954. 11 refs.

A case is reported of intracranial teratoma in the foetus. The patient in her seventh delivery (she had also had 3 abortions) started her labour 1 month prematurely. It proceeded for 14 hours and terminated with the spontaneous vertex delivery of a 3,756 g. living female infant. The infant died after ½ hour. The clinical impression was that of hydrocephalus. At autopsy the infant's head measured 44·5 cm. in circumference. There was an extensive haemorrhage beneath the dura mater and virtual disappearance of the cerebrum. The intracranial contents were a friable, brownish, multicystic, granular, haemorrhagic mass, a thin shell of cortex and much free blood. The tumour mass consisted of a variety of embryonic tissues. The authors discuss 9 other cases reported in the literature.

J. G. Dumoulin

76. **Psychological Aspects of Uterine Dysfunction.**

By W. A. CRAMOND. *Lancet*, **2**, 1241–1245. Dec. 18, 1954. 1 table. 26 refs.

The author points out that the course of labour is governed by the relative size of the foetal head and the pelvis, and by the functional efficiency of the uterus; that uterine dysfunction may occur without mechanical difficulty, and that such dysfunction is more common in first than subsequent labours. In Aberdeen it was found that uterine dysfunction increases approximately eightfold as the age rises from 15–19 years to 35 years or more; and that the incidence was 0·9 per cent at 39–41 weeks' gestation and 3·4 per cent after the 41st week. It has been postulated that fear causes neuromuscular incoordination of the uterus and hence prolongation of labour, therefore the author has investigated the psychological factors in 50 patients who had experienced severe uterine dysfunction and contrasted with 50 controls

whose labour had been normal. All the patients in the dysfunction group were delivered by either Caesarean section or forceps, whereas 47 of the control group were delivered spontaneously and the remaining 3 by low forceps. No essential difference was found between the two groups in respect of the personality types found in the patient's parents. In each group there existed between parents and patient as much warm love and regard as there were unhealthy attitudes of undue attachment or rejection. In 10–15 per cent of each group there had been good instruction and sound attitudes had been inculcated by the mother. Rejection of the feminine rôle and the presence of masculine strivings seemed to occur with the same frequency in each group. No significant difference was found in the two groups in psychosexual adjustment and development; in the frequency of dreams in pregnancy; in the amount of anxiety in pregnancy; in behaviour in labour; in their attitude to breast feeding; in psychopathological trends; or in the incidence of previous psychoneurosis. The essence of the "dysfunction temperament" seems to be in a tendency towards peptic ulceration, little overt anxiety in the presence of an unfamiliar situation with less tremor or sweating, and a bias towards rigid convention. The dysfunction temperament occurred in just over half the cases of dysfunction as compared with 12 per cent of the controls so that it is not the only factor predisposing to disordered uterine action.

The author concludes that uterine dysfunction is of multiple aetiology where age, prolongation of gestation period, the occipito-posterior position and personality all play a greater or lesser part in any one case. He maintains that there is little or no scope for psychotherapy during pregnancy in the prevention of uterine dysfunction.

H. H. Fouracre Barns

77. **The Relief of Pain in Labour.**

By G. D. Read. *West. J. Surg. Obstet. Gynec.*, **62**, 591–597. Dec. 1954.

The author reiterates that the pain of normal labour is due to tension caused by fear and that the fear-tension-pain syndrome cannot be cured by sedative drugs alone. The first principle of the relief of pain in childbirth is progressive education of the young and coupled with this is the need for education of the pregnant woman throughout the antenatal period; the more the patient knows about normal labour, the less she will fear it. Attention must be paid to the education of those giving antenatal instruction and of labour-ward staff as they may, unwittingly, alarm patients and the intensity of discomfort often varies with the skill and understanding of the labour-ward sister. The role of the obstetrician is also reviewed and consideration of the psychosomatic manifestations of parturition urged. The relief from fear and pain are regarded as a necessity for the survival of the cultural standards of the race as surely as strength of arms is necessary for the survival of a nation.

[This paper is virtually an abstract of the 2nd edition of Mr. Read's *Childbirth Without Fear*.]

D. C. A. Bevis

LACTATION

78. **Placenta as a Lactagogon.**

By E. Soyková-Pachnerová, V. Brutar, B. Colová and E. Zvolská. *Gynaecologia, Basel*, **138**, 617–627. Dec. 1954. 36 refs. [In English.]

Almost all mammals in their natural state eat their placentas and in general their milk supply is sufficient for the needs of their young. The effect of administration of placenta to women was thus tried, with special reference to its effect on lactation. Healthy human placenta was therefore "nebulized" and the mothers took it without complaint and with no secondary symptoms. Of 210 women who ate placenta, 71 showed very good results, 110 good results and 29 negative results as regards lactation. Enlargement of the breasts was evident 2 days after the full dose was taken and secretion of milk started about 24 hours later. Cows who eat their placenta yield one litre more milk per day than those who did not have access to their placenta.

A controlled experiment was carried out using dried beef, to exclude the possible lactogenic effect of protein in placenta. The results showed that it is not protein which is responsible. The question of hormone influence from eating placenta is still an open one.

This method of treating deficient lactation appears to be worthy of notice. Placenta is easily obtained and in the author's experience is successful in the majority of women. The cases chosen for treatment were those in which unsuccessful lactation was to be expected.

Josephine Barnes

79. **Clinical and Chemical Studies in Human Lactation. IX. Breast-feeding in Hospital.**

By F. R. Hytten. *Brit. med. J.*, **2**, 1447–1452. Dec. 18, 1954. 9 figs. 18 refs.

The author studied breast-feeding in hospital in 6,456 married women delivered of single and surviving infants in the Aberdeen Maternity Hospital during 1951–53. For first pregnancies the hospital population was reasonably representative of the total Aberdeen population, but there was more selection in higher parities. There were 84·5 per cent who left hospital fully breast-feeding, 71·1 per cent left hospital without any difficulty, and 13·4 per cent after some initial difficulty. There were 2·7 per cent who left partly breast-feeding, and 12·8 per cent were discharged with the baby artificially fed.

The causes of the failures were tabled. Poor lactation was the most important in both primiparae and multiparae. The proportion of failures decreased up to and including the third pregnancy, followed by an increase in higher parities. Breast engorgement, everted and sore nipples were much commoner in primiparae. There was a marked correlation between age and success in breast feeding, associated with the increase in poor lactation with advancing age.

There was a significant association between the mother's general physique and health and her breast-feeding performance in hospital, due chiefly to an increased incidence of "ill babies" in the poorer physique

group, and only slightly to an increase in poor lactation as the primary cause. The upper social groups showed only a slightly higher rate of successful lactation, probably due to the higher proportion of older primiparae.

There was a higher incidence of artificial feeding in those delivered by forceps and Caesarean section due chiefly to poor lactation rather than an "ill baby". Pre-eclamptic toxaemia seemed a cause of increased failure, both from an "ill baby" and poor lactation.

Poor lactation was responsible for 40 per cent of artificial feeding at the time of discharge from hospital. "Ill baby" accounted for 16·6 per cent of failures, maternal opposition for 14·7 per cent and poor nipples for 10·5 per cent.

Sore nipples, breast engorgement, "poor feeder" and maternal disease were much less important, and together contributed to less than 20 per cent.

Eileen Wilson

INFANT

80. The Trend of Changes in Causes of Perinatal Mortality.

By E. L. POTTER. *J. Amer. med. Ass.*, **156**, 1471–1474. Dec. 18, 1954. 7 refs.

At the Chicago Lying-in Hospital perinatal mortality is defined as including all products of conception weighing over 400 g. that have been born dead or that have died in the first 10 days of life. The general causes may be grouped under the following headings: (1) malformations; (2) erythroblastosis; (3) anoxia; (4) trauma; (5) prematurity; (6) infection; (7) abnormal pulmonary function; (8) miscellaneous, including maternal toxaemia and diabetes.

It is almost always possible to arrive at a probable cause for a perinatal death provided that the autopsy has been performed by a pathologist experienced in perinatal pathology and that an adequate clinical history is available. The general causes of perinatal mortality are the same today as they have been through the centuries and they are similar throughout the world. The differences are in the frequency with which the individual causes occur.

Data are given of neonatal mortality rates during the first 14 days of life from the Johns Hopkins Hospital, the Sloane Hospital for Women, and the Chicago Lying-in Hospital over a period of 30 years. Combined mortality for foetuses and for infants less than 4 weeks old has fallen in the United States from 79·1 per 1,000 live births in 1922 to 43·4 per 1,000 in 1950. All causes of perinatal deaths have decreased except malformations and erythroblastosis. Syphilis has largely disappeared as a cause of death while trauma and anoxia associated with labour have shown more decrease than any other cause. The author attributes these changes primarily to improvement of conditions and skill surrounding the patient during labour, but prenatal and postnatal care of the infant have also contributed. The incidence of premature delivery does not seem to have changed during the last 20 years, but survival rates have considerably improved.

D. W. James

81. Increased Plasma Bilirubin in Newborn Infants in Relation to Birth Weight.

By B. H. BILLING, P. G. COLE and G. H. LATHE. *Brit. med. J.*, **2**, 1263–1265. Nov. 27, 1954. 16 refs.

The increased incidence of "physiological" jaundice in premature infants and the possibility of death from kernicterus unassociated with haemolytic disease in such babies prompted an investigation at Queen Charlotte's Hospital of the plasma bile pigment levels. Cases were selected for study purely by birth weight except that those showing any abnormal features other than unusual size were excluded.

The total series comprised 49 infants and they were divided into 8 groups according to weights between 2·5 and 10·5 pounds, not more than 9 nor less than 3 being in each group. Nineteen were "premature", weighing 5·5 pounds (2·5 kg.) or less. Plasma bile pigment estimations were usually made daily from heel-prick samples until it appeared that the peak level had passed.

Results showed that concentrations of plasma bile pigment are consistently high in small neonates and levels of 12–15 mg. per 100 ml. are not uncommon. It was also apparent that in these small infants the period of rise in level is prolonged, as is the time for return to a lower level after the peak, so that the tissues of small infants are exposed to higher concentrations of bile pigment for a longer period than are those of larger babies. Investigation of the type of pigment showed that the predominant pigment behaved on the chromatogram like bilirubin and the direct-reacting bile pigments were considered to be 5–10 per cent or less.

With a high bilirubin level, the liver's capacity to excrete pigment is estimated to be 1–2 per cent of normal. It is postulated that, in the later weeks of foetal life, an adequate hepatic excretory function develops so that the specific defect in the newborn infant of bile pigment metabolism may be a reduced capacity of the liver to transform bilirubin to direct-reacting bile pigment. The premature or retarded baby is born with an incompletely developed liver function. It is this that causes "physiological" jaundice which should be regarded as an essentially abnormal condition.

Prematurity is thus a second condition in which the tissues are exposed to high concentrations of bilirubin.

Doreen Daley

GYNAECOLOGY

82. Vitamins P, C and Niacin for Dysmenorrhoea Therapy.

By A. P. HUDGINS. *West. J. Surg. Obstet. Gynec.*, **62**, 610–611. Dec. 1954. 3 refs.

The author uses niacin (nicotinic acid) for the treatment of disabling dysmenorrhoea; 100 mg. every morning and evening, with 100 mg. every 2–3 hours during the cramping period, is the basic dosage but this may be increased 50–100 mg. or more to maintain flushing with each dose; pain relief is more apparent with flushing and patients should be told that flushing or itching with occasional slight dizziness may be expected about 15 minutes after

taking the tablets and that these symptoms will last for about 15 minutes. Rutin (vitamin P) 60 mg. and ascorbic acid 300 mg. increase the effectiveness of the niacin. In most cases therapy is not effective unless followed for 7–10 days before bleeding begins. The therapy is considered to be nutritional and to improve capillary permeability.

The patients, followed continuously for 3 years, numbered 80 and the treatment is claimed to be effective in 90 per cent.

D. C. A. Bevis

83. **An Amido-Nitrothiazole for Trichomoniasis.**

By S. R. M. Bushby, R. D. Catterall and M. Williamson. *Brit. med. J.*, **1**, 78–80. Jan. 8, 1955. 2 tables. 8 refs. (28 refs. in table 1).

As an antitrichomonal drug, 2-formamido-5-nitrothiazole, "aroxine", has 100 times greater activity *in vitro* than acetarsol and animal experiments show that it is of low toxicity.

A clinical trial was conducted at the Whitechapel Clinic. Series 1 (10 cases) were treated for 7 days and Series 2 (38 cases) for 14 days with 2 foaming pessaries, each containing 100 mg. inserted each night. All these cases had relapsed after other treatment. Series 3 consisted of 98 cases not previously treated at the clinic. Alternate cases were given acetarsol or the above pessaries. Cases were considered cured if there was no clinical or bacterial evidence of recurrence for 3 menstrual cycles after cessation of treatment. Results showed no cures in Series 1, 3 in Series 2, and 5 in Series 3 treated with the drug and 6 in the control group who had had acetarsol. The defaulter rate was about 50 per cent in all groups. There was only 1 case of sensitization to the drug and the irritation and oedema promptly responded to antihistamines.

The authors conclude that the drug is no more effective than acetarsol in preventing relapse, in spite of its great potency *in vitro*, but its low toxicity recommends it as a suppressant.

Doreen Daley

84. **Spontaneous Small Intestine-Cervix and Small Intestine-Bladder Fistula.** (Spontane Dünndarm-Cervix- und spontane Dünndarm-Blasen-Fistel.)

By C. Müller. *Gynaecologia, Basel*, **138**, 594–603. Dec. 1954. 1 fig. 10 refs.

An account is given of the incidence, aetiology, pathological anatomy, symptomatology, diagnosis, treatment and prognosis of vesico-intestinal fistula. Small intestine-bladder fistulas are less common than those between the large intestine and the bladder.

A case report is given of a woman who developed a fistula between the cervix and the small intestine following peritoneal tuberculosis and, later, subtotal hysterectomy. This fistula was successfully closed by the vaginal route in 1948. In 1952 a fistula developed between the small intestine and the bladder. This was closed successfully by means of an abdominal operation which included resection of several loops of small intestine.

Josephine Barnes

85. **The Treatment of Gynaecological and Obstetrical Fistulas.** (Zur Behandlung von gynäkologischen und geburtshilflichen Fisteln.)

By P. Werner and J. Sederl. *Gynaecologia, Basel*, **138**, 575–593. Dec. 1954.

This is a long review of the cause and treatment of vesical, ureteric and rectal fistulae based on a large series of cases.

In the whole series there were 66 vesico-vaginal fistulas, 38 uretero-vaginal fistulas and 27 recto-vaginal fistulas; of these, 4 vesical fistulas, 22 ureteric fistulas and 13 rectal fistulas closed spontaneously. The rest were successfully dealt with by operation.

Josephine Barnes

86. **Torsion of a Fallopian Tube.**

By T. M. Abbas. *Lancet*, **1**, 128–129. Jan. 15, 1955. 9 refs.

The author reports the case of torsion of the left Fallopian tube which previously was apparently normal. The difficulty in making a correct pre-operative diagnosis is stressed. Clinically there is sudden severe pain in an iliac fossa accompanied by nausea and vomiting, and occasionally uterine bleeding. The author advocates aspiration of the pouch of Douglas to determine the presence of intraperitoneal serosanguineous fluid.

[This appears to be an unnecessary and dangerous procedure.]

H. H. Fouracre Barns

87. **A New Therapy for Prevention of Post-operative Recurrences in Genital and Breast Cancer: A Six-years Study of Prophylactic Thyroid Treatment.**

By A. A. Loeser. *Brit. med. J.*, **2**, 1380–1383. Dec. 11, 1954. 3 tables, 21 refs.

From personal observation and statistical analyses by himself and others, the author came to the conclusion that the incidence of breast and genital cancer is far lower in association with allergic and hyperthyroid conditions than if a woman is hypothyroid or has had operative treatment for goitre. Research work by Dr. Feldberg at Mill Hill on the histamine content of skin showed a quantitative relationship between the amount of thyroid in the human body and the intracellular deposition of histamine. High thyroid levels were associated with more histamine and with low blood lipid levels. As intracellular protein-bound histamine is regarded as a defence hormone against cancer, massive thyroid therapy should slow down cancer growth.

Since 1948, thyroid extract in daily dosage varying between 1 and 5 gr. has been given to patients who had had radical surgery, often followed by irradiation, for genital or breast cancer. Four women so treated (2 with genital and 2 with breast lesions) are clinically cured 5 or more years post-operatively, although the original cancer was extensive. Of 14 other cases treated for more than 4 years after mastectomy, only 1 has had a recurrence.

The author considers that these results indicate trial of thyroid therapy on a larger scale.

Doreen Daley

88. **Adenocarcinoma of the Cervix Uteri.**

By H. W. BAKER, C. B. BRACK and R. J. DICKSON. *Obstet. Gynec.*, **6**, 664–669. Dec. 1954. 12 refs.

In the period 1940–1948 31 cases of adenocarcinoma of the cervix were seen at Johns Hopkins Hospital, Baltimore. During the same period there were 522 cases of epidermoid cancer of the cervix. The authors compare the 5-year survival rates in the two groups and find them comparable in all stages, except Stage 2 (although the difference in this group is not very significant statistically). They believe that radium and X-ray therapy appear to give as satisfactory results for Stage 1 adenocarcinoma as for epidermoid carcinoma, although this treatment does not seem to be adequate for the more advanced stages. Where symptoms had been present more than 4 weeks when the diagnosis was made, the prognosis was poor.

J. G. Dumoulin

89. **Pseudomenstruation from Post-hysterectomy Vaginal Vault Endometriosis.**

By T. H. GREEN and J. V. MEIGS. *Obstet. Gynec.*, **6**, 622–634. Dec. 1954. 5 figs. 15 refs.

This article concerns vicarious menstruation from areas of endometriosis in the vaginal vault following hysterectomy. Details are given of 12 cases. In 10 of the cases endometriosis had been found elsewhere in the pelvis at the time of laparotomy. Fibroids with cervicitis and hydrosalpinges were the diagnoses at operation in the other 2 cases. The vaginal bleeding may be cyclical, but it is not always so, particularly when the patient is approaching the menopause. The differential diagnosis includes healing granulations at the vaginal vault, atrophic vaginitis, the rare lesion of vaginal adenosis and vaginal carcinoma. In endometriosis bluish or red nodules in the vaginal apex, or the presence of palpable nodularity may be clues to the diagnosis. Punch biopsy is not a very satisfactory method of obtaining histological material as the lesion is usually not easily accessible. Vaginal endometriosis probably arises as an extension from a lesion in the rectovaginal septum. Primary vaginal endometriosis is very rare and can usually be shown to have followed simple surface implantation.

Treatment consists of simple reassurance and periodic observation. In cases where the symptoms are worrying, X-ray therapy may be used. The lesions invariably regress at the menopause.

J. G. Dumoulin

90. **Treatment of the Vaginal Portion of the Cervix with Electro-cauterization.** (Koagulationsbehandlung der Portio.)

By W. SCHELLENBERG. *Gynaecologia, Basel*, **138**, 518–528. Nov. 1954. 3 figs. 16 refs.

The results of electrocauterization of the cervix in 144 cases are reported. In 53 of these the newly regenerated squamous epithelium was studied by means of Schiller's iodine test. In 33 cases normal iodine positive epithelium developed at the site of cauterization. In 4 cases it was only slightly stained and in 16 it was iodine negative.

Josephine Barnes

91. **Surgery of the Double Uterus. Hemi-hysterectomy and Parietal Hysterosympexy.** (Chirurgie au niveau d'utérus double. Hémi-hystérectomie et hystérosympexie pariétale.)

By R. BOURG and G. LAMBERT. *Gynéc. Obstét.*, **52**, 137–143. 1954. 9 figs. 9 refs.

Ever since hysterosalpingography has been practised with greater frequency for such conditions as dysmenorrhoea or pelvic pain, the incidence of the congenitally abnormal uterus has apparently increased in proportion. The clinical condition itself may remain dormant, even although several confinements have occurred previously.

HEMI-HYSTERECTOMY

Frequently the salpingogram reveals hypoplasia of one horn and rarely a lesion of one or both tubes. In the young woman the indications for the operation must be finally concerned with eventual successful conception. With this in view the removal of one hypoplastic horn must be considered the best thing to do, if it is remembered that any pregnancy in such a genuinely hypoplastic horn rarely, if ever, goes to term. Indications for operating following salpingography in cases of double uterus are multiple: (1) absence of any cervical canal; (2) dysmenorrhoea; (3) ruptured pregnancy; (4) certain rare types of haemorrhage; (5) severe parametritis.

The writers have been struck by the high incidence of fibroids complicating these cases of congenitally abnormal uterus but the numbers seem too small to be significant.

As regards the future, three types of procedure come under discussion in the treatment of double uteri:

1. Cavity sympexy according to Strassmann's technique.
2. Hemi-hysterectomy.
3. Parietal hysterosympexy, i.e., union of the medial surfaces of the two uteri.

D. Maxwell

92. **A Comparative Study of Total and Subtotal Hysterectomy in the Treatment of Uterine Fibroids.**

By P. WETTERDAL. *Acta obstet. gynec. scand.*, **33**, 350–359. 1954. 3 figs. 21 refs.

This study, coming from the Women's Clinic, Sabbatsberg Hospital, Stockholm, was prompted by the fact that in Sweden "subtotal hysterectomy remains on the whole the method of choice, being technically easier and less traumatizing", whilst total hysterectomy is becoming the routine procedure in an increasing number of non-Swedish hospitals.

Of 772 cases of fibroids treated by subtotal hysterectomy during the years 1940 to 1952, 6 patients died after the operation, the mortality being $0{\cdot}8 \pm 0{\cdot}3$ per cent. Of 55 cases of fibroids treated by total abdominal hysterectomy, 2 patients died, a mortality of $3{\cdot}6 \pm 2{\cdot}6$ per cent. No death occurred in 100 cases of fibroids submitted to vaginal hysterectomy. The difference between the mortality percentages did not exceed the product of twice the mean error; thus mortality is no guide to the choice of the operative method in a given case.

The incidence of post-operative pyrexia (a rectal temperature of over 38° C. persisting for over 3 days) was higher in cases of fibroids treated by total abdominal hysterectomy than in those treated by the subtotal operation; the difference exceeded the product of twice the mean error but was less than the product of 3 times the mean error; thus it was not statistically significant. On the other hand, the higher incidence of post-operative pyrexia after vaginal hysterectomy as compared with that after subtotal hysterectomy was statistically significant.

Total hysterectomy involved a statistically significant longer post-operative stay in hospital than subtotal hysterectomy. [Unfortunately, the 2 groups are not comparable because the subtotal hysterectomy group includes only cases of fibroids, whilst the other group comprised a number of cases of carcinoma.]

Simultaneous adnexectomy and/or appendectomy did not influence either post-operative pyrexia or length of hospitalization.

The author collected from a survey of the literature 40,164 cases of subtotal hysterectomy; in 206 or 0·5 per cent carcinoma developed in the cervical stump, the incidence given by individual authors varying between 0·3 and 2 per cent. In the author's own 772 cases, cervical carcinoma developed in 4, or 0·5 per cent, 1 to 2, 2 to 3, 4 to 5, and 8 to 9 years after the operation respectively. The author thinks that fear of development of malignancy in the cervical stump is exaggerated.

It is concluded that menopausal women should preferably be treated by total hysterectomy, combined with oöphorectomy. In women of reproductive age, subtotal hysterectomy should be the method of choice provided that there is proof of absence of cervical malignancy (Papanicolaou's test, curettage). However, in the hands of an experienced surgeon, total hysterectomy carried no more dangers to the patient than does subtotal hysterectomy.

N. Alders

93. Pharmacological Effect of Various Drugs on Micturition.

By R. E. Van Duzen. *J. Amer. med. Ass.*, **156**, 1393–1396. Dec. 11, 1954. 6 refs.

Drugs affecting the sensory nerves of the bladder are not very important, and those affecting the motor nerves may be either adrenergic or cholinergic. Owing to the conflicting theories on the anatomy and nerve supply of the bladder the mode of action of drugs has been difficult to interpret. Ephedrine and epinephrine are considered to be adrenergic, but although ephedrine may aid in stress incontinence it is the action on the cerebral centres that is beneficial. The cholinergic drugs act by inhibiting the destroying action of choline esterase and prolonging the action of acetylcholine. Useful drugs stimulating micturition in this way are Prostigmin, Mercholyl, Doryl, Urecholine and Pitressin.

Antihistamine drugs occasionally produce urinary symptoms as a side effect and certain other commonly used drugs may affect the bladder secondarily. Morphine stimulates the detrusor muscle of the bladder and may, when combined with post-anaesthetic effects, be a cause of post-operative retention. Methantheline (Banthine) blocks cholinergic transmission and may cause retention. Apresoline has also been known to cause complete retention. Oestrogens have been advocated for frequent and urgent micturition in women but any effect is probably due to the action on the erectile tissue. The author concludes that the choline derivatives are the most important drugs directly affecting micturition.

D. W. James

NOTICES

THE JOURNAL OF OBSTETRICS AND GYNAECOLOGY OF THE BRITISH EMPIRE is published under the direction of the Royal College of Obstetricians and Gynaecologists. All business correspondence should be addressed to the *Journal of Obstetrics and Gynaecology of the British Empire*, 58 Queen Anne Street, London, W.1.

SUBSCRIPTION RATES

The Journal is published bi-monthly on or about the 21st of February, April, June, August, October, December and the Annual Subscription rates, due on 1st January, covering 1 volume (6 issues) are:

	£	s.	d.
Great Britain, Northern Ireland and Eire	3	5	0
Dominions, Colonies and Foreign Countries: Surface Mail	3	15	0
Air Mail	5	17	6

Subscriptions are only accepted for complete volumes.

Remittances are payable to:

The Journal of Obstetrics and Gynaecology of the British Empire,
58 Queen Anne Street, London, W.1.

Banker's Orders should be made payable to the Journal account at Barclays Bank, Vere Street, Cavendish Square, London, W.1.

Overseas payments should be by Banker's draft payable at sight in London.

EDITORIAL NOTICES

The Editor is: Professor James Young, D.S.O., M.D., F.R.C.S., F.R.C.O.G., Ashfield, Balcombe Road, Haywards Heath, Sussex.

PUBLICATION

Original articles for publication are invited and should be sent to the Editor. They are considered for publication on the understanding that they are contributed to this Journal solely. Reproduction elsewhere will usually be approved if permission is obtained from the Editor and Author and the customary acknowledgment made. The Royal College of Obstetricians and Gynaecologists cannot be held responsible for the views expressed in the Journal.

Blocks will normally be held by the Printers for two years after which they will be destroyed.

BOOKS FOR REVIEW

Books for review should be sent to the Editor, Professor James Young, Ashfield, Balcombe Road, Haywards Heath, Sussex.

Directions to Contributors

Authors are advised to keep a copy of all manuscripts. Proofs will be submitted to authors resident in the United Kingdom, but to avoid delay or loss the proofs of authors resident abroad will be corrected by the editorial staff, unless the authors wish to delegate the work to a representative in this country.

PRESENTATION OF MANUSCRIPT

Double spaced typescript (not carbon copies) should be submitted. Italics in the text should in general be reserved for words in a foreign language and as little as possible used to indicate emphasis.

Proper scientific names giving both genus and species should be italicized, with an initial capital and contraction for the genus only after a full spelling at the first mention, thus:

Clostridium welchii followed by *Cl. welchii*; *Bacterium coli —Bact. coli*; *Mycobacterium tuberculosis—Myco. tuberculosis; Corynebacterium diphtheriae—C. diphtheriae.*

Each sentence should have its proper components thus:

"*Progress:* The patient continued to improve," NOT
"*Progress:* Went downhill."

The author's name, his decorations, degrees and relevant diplomas should appear at the head of the paper together with his appointment at the time of preparation of the text.

TABLES AND ILLUSTRATIONS

Tables should be numbered in Roman numerals (Table I, Table II, etc.) and set out on sheets separate from the text, with indications as to where the author desires them to be placed. Illustrations, too, should be kept separate from the text and numbered in Arabic numerals, Fig. 1, Fig. 2, etc. Each figure should have a reference in the text and a descriptive legend to be printed underneath. This legend should be typed on an attached sheet and not written on the back of the illustration. The lines in charts should not be in colours but in black, and when graph paper is used the ruling should be grey or faint blue and *not* brown, red or green. The magnification of microscopical illustrations should be stated (e.g. ×250). X-ray films should not be submitted unless the author is not in a situation to have these printed, when the Journal will undertake to have this done. If the films promise poor reproduction the author is advised to send line tracings of the appearances instead. Authors may be required, at the Editor's discretion, to contribute to the cost of reproducing tables and illustrations.

ABBREVIATIONS

These should be avoided as far as possible. "Per cent" should be used instead of the symbol "%" and such forms as T.B., R.B.C., B.P., P.E.T., A.P.H. eschewed.

Dates should be given as 10th May, 1946, and *not* 10.V.46. Numbers should be in the form of numerals and not words except when beginning a sentence, thus "Fifteen patients out of a total of 60 exhibited," etc. The official rather than the proprietary names of drugs must be used. The Journal convention is gr. for grains; g. for grammes; Kg.; ml. (*not* c.c. or c.cm.); mg.; pounds (*not* lb.); ounces (*not* oz.), etc., and wherever suitable the metric equivalent of an English measure should be given, for example, when recording pelvic measurements, size and weight of babies, tumours, etc.

When comparable figures are given, either the English or the metric mode must be followed, thus: the excretion of urine/24 hours should be shown in ml. (and not ounces) when the urinary or blood-urea is given in g./100 ml.

REFERENCES

In the text the author's name should be given, with the date of publication and the list of authors quoted put at the end of the text in alphabetical order as in the Harvard Scheme: Author's name, initials, year of publication (in brackets), name of journal (*italics* abbreviated), volume number (underlined) and page number. In the case of books the order is: Author's name, initials, year of publication, full title (*italics*), edition, publisher and place of publication, page, thus:

Brown, H. E., and Jones, B. K. (1943): *J. Obstet. Gynaec. Brit. Emp.*, **2**, 128.

Sampson, P. (1940): *Obstetrics for Midwives*. 2nd edition. Fraser, London. p. 9.

REPRINTS

The issue of free reprints to contributors is discontinued, but a copy of the issue in which the article appears will be sent to any contributor who is not a subscriber. Reprints can be purchased by arrangement with the printers if application is made when the corrected proof is returned or, in the case of overseas contributors, when the manuscript is submitted.

Terramycin was discovered after screening 124,756 soil samples in the Pfizer Research Laboratories.

in OBSTETRICS and GYNAECOLOGY

Pfizer

Terramycin*

BRAND OF OXYTETRACYCLINE

Oral Terramycin treatment produces therapeutic antibiotic concentrations in the blood, both maternal and fœtal[1]. Obstetrical and gynæcological infections respond well to Terramycin[2, 3, 4, 5] because of its rapidly attained therapeutic concentrations in blood, urine and tissues, and its activity against a wide variety of micro-organisms.

References: 1. *Obst. Gyn.* (New York) (1953) 1, 302. 2. *J. Obst. Gyn. Brit. Emp.* (1954) 61, 145. 3. *Geburtsh. und Gynäkol.* (1953) 139, 65. 4. *Canad. med. Ass. J.* (1952) 66, 151. 5. *Bull Marg. Hague Mat. Hosp.* (1952) 5, 67.

Pfizer *Worlds Largest Producer of Antibiotics*

Full literature is available and will be supplied on request

PFIZER LTD · FOLKESTONE · KENT · tel: Folkestone 51771

*Trade Mark of Charles Pfizer & Co.Inc.

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD
109 KINGSWAY LONDON WC2 AND ASHFORD KENT

THE JOURNAL OF OBSTETRICS AND GYNAECOLOGY OF THE BRITISH EMPIRE

Vol. LXII APRIL 1955 No. 2

CONTENTS

A Study of the Effects of Dihydroergotamine on the Intact Human Uterus
Part I: "Sympatholytic" Properties. *William J. Garrett, M.B., B.S.* 145
Part II: "Oxytocic" Properties. *Mostyn P. Embrey, M.D., B.Sc., F.R.C.S.E., M.R.C.O.G., and William J. Garrett, M.B., B.S.* 150

Uterine Activity and Electrical Response 155
E. C. Halliday and O. S. Heyns

The Natural History of Pelvic Tuberculosis. Being the Material Used for the Eighteenth William Blair-Bell Memorial Lecture 162
Tom Barns, M.A., D.M., M.R.C.O.G.

Radium Menopause or Hysterectomy. Part I: The Effects of the Radiation Menopause—A Controlled Study 176
A. C. Turnbull, M.B., M.R.C.O.G.

The Treatment of 850 Cases of Simple Uterine Haemorrhage by Intra-uterine Application of Radium 187
Wallace Barr, B.Sc., M.B., M.R.C.O.G., and Alexander A. Charteris, M.B., D.P.H., F.R.F.P.S.G., F.F.R.

Phaeochromocytoma and the Obstetrician 195
Sir Arthur A. Gemmell, M.C., T.D., P.R.C.O.G.

Phaeochromocytoma in a Pregnant African Woman 203
J. N. P. Davies, M.D., and Coralie Rendle Short, M.B., Ch.M., F.R.C.O.G.

A Preliminary Series of Cases of Uterine Hypoplasia Treated by Local Injection of an Oestrogenic Emulsion 205
Sara Field-Richards, M.B., M.R.C.O.G.

Salpingectomy or Salpingo-oöphorectomy? 214
T. N. A. Jeffcoate, M.D., F.R.C.S.E., F.R.C.O.G.

Trends in the Risks of Childbearing and in the Mortalities of Infants During the Last 30 Years 216
Charlotte A. Douglas, O.B.E., M.D., D.P.H., F.R.C.O.G.

Choriocarcinoma. A Report of Two Cases with Unusual Features 232
John Peel, M.A., B.M., B.Ch., F.R.C.S., F.R.C.O.G., John Dawson, M.C., M.D., M.R.C.P., and Gordon Mather, M.B., M.R.C.P.

Hydatidiform Mole and Chorionepithelioma. Including Case Report 239
P. Cowell Barkla, V.R.D., M.B., F.R.C.S.E., M.R.C.O.G.

The Vertebral Venous Drainage of the Pelvis 244
T. N. A. Jeffcoate, M.D., F.R.C.S.E., F.R.C.O.G.

Mono-amniotic Twin Pregnancy. Two Cases 247
Gordon M. Parkin, M.B., B.S., D.G.O.(Syd.)

The Rural Scene Surveyed. An Obstetrical Review 249
R. F. Lawrence, E.R.D., M.D., M.R.C.O.G.

Oestrogen Therapy in Missed Abortion and Labour 256
R. H. Martin, M.B., Ch.B., M.R.C.O.G., and D. N. Menzies, M.B., Ch.B., M.R.C.O.G.

Recurrent Vomiting in Pregnancy. Three Cases of Hiatus Hernia 259
D. F. P. Gordon, F.R.C.S.(Ed.), M.R.C.O.G.

Pregnancy Complicated by Diabetes 262
G. O. Richardson, M.D., M.R.C.P., Linton Snaith, M.D., M.S., F.R.C.S., F.R.C.O.G., and J. C. Sibley, M.D., M.R.C.P., F.R.C.P.(Can.)

The Effect of Hodgkin's Disease on Pregnancy and Fertility 266
H. G. Frank, M.D., M.Rad.

Chronic Endometritis and Plasma Cell Infiltration of the Endometrium 269
J. M. Brudenell, M.B., B.S.

Premature Babies in the Tropics 275
Derek Llewellyn-Jones, M.B., M.A.O.

Fibrinogenaemia in an Iso-sensitized Mother Carrying a Dead Foetus 280
Louis J. Quinn, B.A., M.D., M.R.C.O.G., F.R.C.S.(C.), and J. A. Harper, M.D.

Caesarean Section in Eclampsia 283
Dr. M. K. Krishna Menon, B.A., M.D.

Bowen's Disease of the Vulva. Report of 2 Cases 288
F. Hamilton Leckie, M.C., T.D., L.R.C.P., M.R.C.O.G.

Errors in the Determination of Urinary Pregnanediol 291
M. G. Coyle, M.B., F. L. Mitchell, B.Sc., Ph.D., C. S. Russell, F.R.C.O.G., and C. G. Paine, M.D.

Palmar Sweating in Pregnancy 298
P. C. B. MacKinnon, M.B., Ch.B., and I. L. MacKinnon, M.B., Ch.B.

Royal College of Obstetricians and Gynaecologists 300
Tumour Registry 301
Reports of Societies 302
Book Reviews 309
Review of Current Literature 311
Notices 320

AND
PIRE
No. 2

145
150
155
162
176
187
195
203
205
214
216
232
239
244
247
249
256
259
262
266
269
275
280
283
288
291
298
300
301
302
309
311
320